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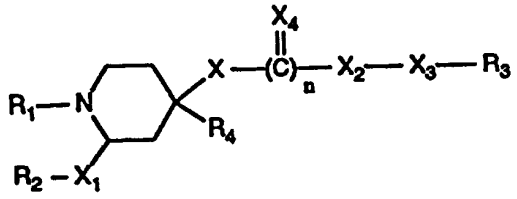
(54) Title: N-BENZOYL-4-OXY/THIO-2-SUBSTITUTED PIPERIDINES AS SUBSTANCE-P RECEPTOR ANTAGONISTS



(I)

(57) Abstract

1,2,4-Trisubstituted piperidine compounds of fomula (I), wherein R_1 is an unsubstituted or substituted aralkyl, aryloxyalkyl, heteroaralkyl, aroyl, heteroaroyl, cycloalkylcarbonyl, aralkanoyl, heteroarylalkanoyl, aralkoxycarbonyl or arylcarbamoyl radical, or is the acyl radical of an α-amino acid that is unsubstituted or N-substituted by lower alkanoyl or by carbamoyl-lower alkanoyl; R_2 is cycloalkyl or an unsubstituted or substituted aryl or heteroaryl radical; R_3 is an unsubstituted or substituted, optionally hydrogenated aryl or heteroaryl radical or, when n is 1, X_2 is imino that is unsubstituted or substituted by lower alkyl or by cycloalkyl and X_3 is lower alkylene, R_3 is lower alkyl or free or esterified or amidated carboxy, R_4 is hydrogen or alkyl; X_1 is methylene, ethylene, a direct bond, a free or ketalised carbonyl group or a free or etherified hydroxymethylene group; X_2 is lower alkylene, imino that is unsubstituted or substituted by lower alkyl or by cycloalkyl, or a direct bond; X_3 is lower alkylene or a direct bond; X_4 is oxo or thioxo; and n is 1 or, when X_2 is lower alkylene and X_3 is a direct bond, n is 0; and the salts thereof, have compound-P-antagonistic properties and can be used as active ingredients of medicaments.

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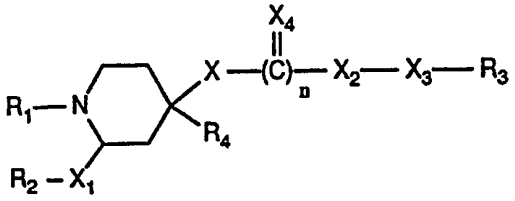
N-BENZOYL-4-OXY/THIO-2-SUBSTITUTED PIPERIDINES AS SUBSTANCE-P RECEPTOR ANTAGONISTS

The invention relates to novel 1,2,4-trisubstituted piperidine compounds of formula I



(I),

wherein

R_1 is an unsubstituted or substituted aralkyl, aryloxyalkyl, heteroaralkyl, aroyl, heteroaroyl, cycloalkylcarbonyl, aralkanoyl, heteroarylalkanoyl, aralkoxycarbonyl or arylcarbamoyl radical, or is the acyl radical of an α-amino acid that is unsubstituted or N-substituted by lower alkanoyl or by carbamoyl-lower alkanoyl,

R_2 is cycloalkyl or an unsubstituted or substituted aryl or heteroaryl radical,

R_3 is an unsubstituted or substituted, optionally hydrogenated aryl or heteroaryl radical or, when n is 1, X_2 is imino that is unsubstituted or substituted by lower alkyl or by cycloalkyl and X_3 is lower alkylene, R_3 is lower alkyl or free or esterified or amidated carboxy,

R_4 is hydrogen, alkyl or aryl,

X is oxy or thio,

X_1 is methylene, ethylene, a direct bond, a free or ketalised carbonyl group or a free or etherified hydroxymethylene group,

X_2 is lower alkylene, imino that is unsubstituted or substituted by lower alkyl or by cycloalkyl, or a direct bond,

X_3 is lower alkylene or a direct bond,

X_4 is oxo or thioxo and

n is 1 or, when X_2 is lower alkylene and X_3 is a direct bond, n is 0,

and to the salts thereof, to processes for the preparation of the compounds according to the invention, to pharmaceutical compositions comprising those compounds and to the use thereof as active ingredients of medicaments.

Aryl, cycloalkyl and heteroaryl radicals, also as constituents of aralkyl, aryloxyalkyl, aroyl, aralkanoyl, aralkoxycarbonyl, arylcarbamoyl, cycloalkylcarbonyl, heteroaralkyl, heteroaroyl and heteroarylalkanoyl radicals, optionally partially hydrogenated heteroaryl radicals, heteroaroyl radicals and the like, may be unsubstituted or substituted, such as mono-, di- or tri-substituted, especially mono- or di-substituted, for example by aromatically bonded lower alkyl, lower alkoxy, phenoxy, halogen, free or esterified or amidated carboxy, cyano, nitro and/or by trifluoromethyl. Aryl, aralkyl, aryloxyalkyl, cycloalkylcarbonyl and aroyl radicals are preferably mono- or di-substituted, such as 3- or 4-mono- or 3,5-di-substituted, as indicated.

Aryl radicals R_2 are, for example, phenyl radicals that are unsubstituted or mono- or di-substituted by lower alkyl, lower alkoxy, halogen, free or esterified or amidated carboxy, cyano, nitro and/or by trifluoromethyl, such as phenyl, 4-lower alkoxy-, such as 4-methoxy-phenyl, 4-nitrophenyl, free or amidated 4-carboxyphenyl, such as 4-carboxy- or 4-carbamoyl-phenyl, 3-trifluoromethylphenyl, 2,4-di-lower alkoxy-, such as 2,4-dimethoxy-phenyl, 2,4-dihalo-, such as 2,4-dichloro-phenyl, or 3,4-dihalo-, such as 3,4-dichlorophenyl.

Optionally hydrogenated aryl radicals R_3 are, for example, phenyl, cyclohexyl, naphthyl or tetrahydronaphthyl radicals that are unsubstituted or mono- or di-substituted by lower alkyl, lower alkoxy, phenoxy, halogen, free or esterified or amidated carboxy, cyano and/or by trifluoromethyl, such as phenyl, cyclohexyl, naphthyl, 3-lower alkoxy-, such as 3-methoxy- or 3-isopropyloxy-phenyl, 4-phenoxyphenyl, 4-lower alkoxy-, such as 4-methoxy- or 4-isopropyloxy-phenyl, 3- or 4-halo-, such as 3- or 4-chloro-phenyl, free or esterified 4-carboxyphenyl, such as 4-carboxy- or 4-lower alkoxycarbonyl-phenyl, 4-cyanophenyl, 3-trifluoromethylphenyl, 3,5-dihalo-, such as 3,5-difluoro-phenyl, or 3,4-dihalo-, such as 3,4-dichloro-phenyl.

Aralkyl radicals are, for example, phenyl- or diphenyl-lower alkyl or naphthyl-lower alkyl that is unsubstituted or substituted in the phenyl or naphthyl moiety.

Aryloxyalkyl radicals are, for example, aryloxy-lower alkyl radicals, such as phenoxy-lower alkyl radicals that are unsubstituted or substituted in the phenyl moiety.

Heteroaralkyl radicals are, for example, heteroaryl-lower alkyl radicals containing as

heteroaryl radical 6-membered monocyclic azaheteroaryl or bicyclic azaheteroaryl consisting of a 6-membered ring and a 5- or 6-membered ring.

Aroyl radicals are, for example, unsubstituted or substituted benzoyl radicals, such as benzoyl, 3-lower alkyl-, 3-lower alkoxy-, 3-halo-, 3-dimethylamino-, 3,5-di-lower alkyl-, 3,5-di-lower alkoxy-, 3,5-dihalo- or 3,5-ditrifluoromethyl-benzoyl, or, less preferably, unsubstituted or substituted naphthoyl radicals, such as 1- or 2-naphthoyl.

Heteroaroyl radicals are, for example, 6-membered monocyclic azaheteroaroyl radicals or bicyclic azaheteroaroyl radicals consisting of a 6-membered and a 5- or 6-membered ring, such as pyridylcarbonyl or quinolinylcarbonyl.

Cycloalkylcarbonyl radicals (cycloalkanoyl radicals) are, for example, unsubstituted or substituted 3- to 8-membered, especially 5- to 7-membered, cycloalkylcarbonyl radicals, such as cyclohexylcarbonyl, 3-lower alkyl-, 3-lower alkoxy-, 3-halo-, 3-dimethylamino-, 3,5-di-lower alkyl-, 3,5-di-lower alkoxy-, 3,5-dihalo- or 3,5-ditrifluoromethyl-cyclohexyl-carbonyl.

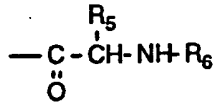
Aralkanoyl radicals are, for example, phenyl- or diphenyl-lower alkanoyl radicals that are unsubstituted or substituted in the phenyl moiety.

Heteroarylalkanoyl radicals are, for example, heteroaryl-lower alkanoyl radicals containing as heteroaryl radical 6-membered monocyclic azaheteroaryl or bicyclic azaheteroaryl consisting of a 6-membered and a 5- or 6-membered ring.

Aralkoxycarbonyl radicals are, for example, phenoxycarbonyl radicals that are unsubstituted or substituted in the phenyl moiety.

Arylcarbamoyl radicals are, for example, N-phenylcarbamoyl radicals that are unsubstituted, or unsubstituted or substituted in the phenyl moiety.

Acyl radicals of α-amino acids that are unsubstituted or N-substituted by lower alkanoyl or by carbamoyl-lower alkanoyl are derived especially from α-amino acids that occur naturally as peptide building blocks and that are optionally lower alkanoylated, for example N-C_2-C_7alkanoylated, such as α-amino acids substituted by acetyl, propionyl, butyryl or pivaloyl. Such acyl radicals are, for example, groups of formula



(Ia),

wherein

R_5 is hydrogen, or a lower alkyl radical, such as a C_1-C_4alkyl radical, that is unsubstituted or substituted by hydroxy, amino, mercapto, unsubstituted or hydroxy-substituted phenyl, carboxy, carbamoyl or by ureido, for example methyl, isopropyl, isobutyl, secondary butyl, hydroxymethyl, mercaptomethyl, 2-methylmercaptoethyl, 3-ureidopropyl, 4-aminobutyl, carboxymethyl, carbamoylmethyl, 2-carboxyethyl, 2-carbamoylethyl, benzyl or 4-hydroxybenzyl, and

R_6 is lower alkanoyl, for example C_2-C_7alkanoyl, such as acetyl, propionyl, butyryl or pivaloyl.

Such an acyl radical may also, however, be the acyl group of a heterocyclic α-amino acid that occurs naturally as a peptide building block, such as prolyl, tryptophanyl or histidinyl.

Cycloalkyl radicals are, for example, 5- to 7-membered cycloalkyl radicals, such as especially cyclohexyl or, less preferably, cyclopentyl or cycloheptyl.

Heteroaryl radicals are, for example, 5-membered monocyclic oxa- or thia-aryl radicals, such as furyl or thienyl, 6-membered monocyclic aza- or diaza-aryl radicals, such as pyridyl or pyrimidinyl, or heteroaryl radicals consisting of a 5- or 6-membered mono- or diaza- or oxa-heteroaryl radical and a 6-membered aryl radical, such as benzofuranyl, for example benzofuran-2-yl or -3-yl, indolyl, for example indol-2-yl or -3-yl, or 1-lower alkyl-, such as 1-methyl-indol-2-yl, benzimidazolyl, for example benzimidazol-2-yl, or quinolyl, for example quinolin-4-yl.

Hydrogenated heteroaryl radicals are especially partially hydrogenated heteroaryl radicals, for example partially hydrogenated heteroaryl radicals consisting of a partially hydrogenated 5- or 6-membered mono- or diaza- or oxa-heteroaryl radical and a 6-membered aryl radical, such as 2,3-dihydroindolyl, for example 2,3-dihydroindol-2-yl or -3-yl, or 1,2,3,4-tetrahydroquinolinyl radicals, for example 1,2,3,4-tetrahydroquinolinyl-4-yl.

Ketalised carbonyl groups are ketalised, for example, by an aliphatic alcohol or dialcohol, such as a lower alkanol or a lower alkanediol and are, for example, di-lower alkoxymethylene or lower alkylenedioxymethylene.

Etherified hydroxymethylene groups are etherified, for example, especially by an aliphatic alcohol, such as a lower alkanol, and are, for example, lower alkoxymethylene.

Unsubstituted or lower alkyl- or cycloalkyl-substituted imino is, for example, imino, N-lower alkylimino or N-cycloalkylimino.

Hereinbefore and hereinafter, lower radicals and compounds are to be understood, for example, as being lower radicals and compounds having up to and including 7, preferably up to and including 4, carbon atoms (C atoms).

Lower alkyl is, for example, C_1-C_7alkyl, preferably C_1-C_4alkyl, such as especially methyl or, less preferably, ethyl, propyl, isopropyl or butyl, but may also be isobutyl, secondary butyl, tertiary butyl or a C_5-C_7alkyl group, such as a pentyl, hexyl or heptyl group.

Lower alkylene is, for example, C_1-C_7alkylene, preferably C_1-C_4alkylene, such as methylene, ethylene, 1,3-propylene, 1,4-butylene or 1,5-pentylene.

Lower alkoxy is, for example, C_1-C_7alkoxy, preferably C_1-C_4alkoxy, such as methoxy, ethoxy, propyloxy, isopropyloxy or butyloxy, but may also be isobutyloxy, secondary butyloxy, tertiary butyloxy or a pentyloxy, hexyloxy or heptyloxy group.

Halogen is, for example, halogen having an atomic number of up to and including 35, such as chlorine or fluorine, also bromine.

Phenyl-lower alkyl that is unsubstituted or substituted in the phenyl moiety is, for example, corresponding phenyl-C_1-C_4alkyl, such as benzyl, 2,4-dichlorobenzyl, 3,5-ditrifluoromethylbenzyl or 2-phenylethyl.

Diphenyl-lower alkyl that is unsubstituted or substituted in the phenyl moieties is, for example, corresponding diphenyl-C_1-C_4alkyl, such as 2,2-diphenylmethyl.

Naphthyl-lower alkyl that is unsubstituted or substituted in the naphthyl moiety is, for example, corresponding naphthyl-C_1-C_4alkyl, such as 1- or 2-naphthylmethyl.

Phenoxy-lower alkyl that is unsubstituted or substituted in the phenyl is, for example, phenoxy-C_1-C_4alkyl substituted by halogen and/or by triazolyl, such as 2-[2-(1H-1,2,4-tri-

azol-1-yl)-4-chloro-phenoxy]ethyl.

Heteroaryl-lower alkyl containing as heteroaryl radical 6-membered monocyclic aza-heteroaryl or bicyclic azaheteroaryl consisting of a 6-membered and a 5- or 6-membered ring is, for example, pyridyl-C_1-C_4alkyl, such as pyridylmethyl, or quinolinyl-C_1-C_4alkyl, such as 4-quinolinylmethyl.

Phenyl-lower alkanoyl that is unsubstituted or substituted in the phenyl moiety is, for example, phenyl-C_1-C_4alkanoyl, such as phenylacetyl, 2,4-dichlorophenylacetyl, 3,5-ditrifluoromethylphenylacetyl or 2-phenylpropionyl.

Diphenyl-lower alkanoyl that is unsubstituted or substituted in the phenyl moiety is, for example, diphenyl-C_1-C_4alkanoyl, such as diphenylacetyl.

Heteroaryl-lower alkanoyl containing as heteroaryl radical 6-membered monocyclic aza-heteroaryl or bicyclic azaheteroaryl consisting of a 6-membered and a 5- or 6-membered ring is, for example, pyridyl-C_1-C_4alkanoyl, such as pyridylacetyl, or quinolinyl-C_1-C_4alkanoyl, such as 4-quinolinylacetyl.

Di-lower alkoxymethylene is, for example, di-C_1-C_4alkoxymethylene, such as dimethoxymethylene, diethoxymethylene, dipropyloxymethylene or dibutyloxymethylene.

Lower alkylenedioxymethylene is, for example, 5- to 8-membered, especially 5- or 6-membered, 1,3-dioxacycloalk-2-yl, such as 1,3-dioxacyclobut-2-yl, 1,3-dioxacyclopent-2-yl (1,3-dioxolan-2-yl), 1,3-dioxacyclohex-2-yl (1,3-dioxan-2-yl) or 1,3-dioxacycloheptyl-2-yl.

Lower alkoxymethylene is, for example, C_1-C_4alkoxymethylene, such as methoxymethylene, ethoxymethylene, propyloxymethylene or butyloxymethylene.

N-Lower alkylimino is, for example, N-C_1-C_4alkylimino, such as methylimino, ethylimino, propylimino, isopropylimino or butylimino, but may also be isobutylcarbamoyl.

N-Cycloalkylimino is, for example, 3- to 8-membered, especially 5- to 7-membered, N-cycloalkylimino, such as cyclohexylimino.

The compounds of formula I are of basic character and are accordingly capable of forming acid addition salts.

Acid addition salts of compounds of formula I are, for example, the pharmaceutically acceptable salts thereof with suitable mineral acids, such as hydrohalic acids, sulfuric acid or phosphoric acid, for example hydrochlorides, hydrobromides, sulfates, hydrogen sulfates or phosphates, or salts with suitable aliphatic or aromatic sulfonic acids or N-substituted sulfamic acids, for example methanesulfonates, benzenesulfonates, p-toluenesulfonates or N-cyclohexylsulfamates (cyclamates).

For isolation or purification purposes, it is also possible to use pharmaceutically unacceptable salts. Only the pharmaceutically acceptable, non-toxic salts are used therapeutically and those salts are therefore preferred.

The compounds provided according to the invention have valuable pharmacological properties. In particular, they exhibit a pronounced antagonistic action towards compound P and have the spectrum of properties typical of compound-P-antagonists. For example, the compounds of formula I and the pharmaceutically acceptable salts thereof inhibit *in vitro* the binding of ^{3}H-compound-P to bovine retina in the radio receptor assay according to H. Bittiger, Ciba Foundation Symposium 91, 196-199 (1982) in concentrations of approximately 0.01 µmol/litre and above. For example, in the case of (2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-(3-quinolylmethoxy)-piperidine, an IC_{50} value of 0.011 µmol/litre is found. The antagonistic action at the human compound-P receptor can be determined in accordance with C.M. Lee *et al.*, J. Neurochem. 59, 406-411 (1992), from the inhibition of the compound-P-induced increase in the inositol monophosphate content in human astrocytoma cells (U-373 MG) in concentrations of approximately 0.01 µmol/litre and above. For example, in the case of (2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-(3-quinolylmethoxy)-piperidine, an IC_{50} value of 0.00076 µmol/litre is found.

Compound P is a naturally occurring undecapeptide of the tachykinin family. It is produced and deposited in sensory neurones of the spinal bone marrow and of the brain in mammals and acts pharmacologically as a neurotransmitter and/or neuromodulator. The compound-P-antagonists of formula I provided according to the invention and the pharmaceutically acceptable salts thereof are metabolically stable and are accordingly outstandingly suitable for the prophylactic and therapeutic treatment of diseases in which

compound P plays an essential role, for example in the case of painful conditions, in migraines, in disorders of the central nervous system, such as anxiety states, schizophrenia and depression, in certain motor disorders, such as Parkinson's disease, in inflammatory diseases, such as rheumatoid arthritis and osteoarthritis, in diseases of the respiratory organs, such as asthma, chronic bronchitis and chronic rhinitis, in diseases of the gastro-intestinal system, such as ulcerative colitis and Crohn's disease, in vomiting, especially chemically induced vomiting, and in hypertension.

The compound-P-antagonists of formula I provided in accordance with the invention and the pharmaceutically acceptable salts thereof are therefore outstandingly suitable for the therapeutic treatment of the mentioned diseases.

The invention relates especially to compounds of formula I wherein

R_1 is a phenyl-, diphenyl-, naphthyl- or fluorenyl-lower alkyl radical that is unsubstituted or substituted in the phenyl moiety by lower alkyl, lower alkoxy, di-lower alkylamino, halogen and/or by trifluoromethyl; a phenoxy-lower alkyl radical that is unsubstituted or substituted in the phenyl moiety by halogen and/or by triazolyl; a heteroaryl-lower alkyl radical containing as heteroaryl radical 6-membered monocyclic azaheteroaryl or bicyclic azaheteroaryl consisting of a 6-membered and a 5- or 6-membered ring; a benzoyl, naphthoyl, fluorenoyl or 3- to 8-membered cycloalkylcarbonyl radical that is unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, di-lower alkylamino, halogen, cyano and/or by trifluoromethyl; a phenyl- or diphenyl-lower alkanoyl radical that is unsubstituted or substituted in the phenyl moiety by lower alkyl, lower alkoxy, di-lower alkylamino, halogen and/or by trifluoromethyl; a heteroaryl-lower alkanoyl radical containing as heteroaryl radical 6-membered monocyclic azaheteroaryl or bi- or tri-cyclic azaheteroaryl consisting of a 6-membered and one or two 5- or 6-membered ring(s); a phenyl-lower alkoxycarbonyl or N-phenylcarbamoyl radical that is unsubstituted or substituted in the phenyl moiety by lower alkyl, lower alkoxy, di-lower alkylamino, halogen and/or by trifluoromethyl; or the acyl radical of an α-amino acid that occurs naturally as a peptide building block and that is unsubstituted or N-substituted by lower alkanoyl or by carbamoyl-lower alkanoyl,

R_2 is 5- to 7-membered cycloalkyl or a phenyl, naphthyl or 6-membered monocyclic azaheteroaryl radical that is unsubstituted or substituted by aromatically bonded lower alkyl, lower alkoxy, halogen, cyano, nitro, carboxy, carbamoyl and/or by trifluoromethyl,

R_3 is an unsubstituted or lower alkyl-, lower alkoxy-, phenoxy-, halogen-, carboxy-,

lower alkoxycarbonyl-, carbamoyl-, cyano- and/or trifluoromethyl-substituted phenyl, cyclohexyl, naphthyl, tetrahydronaphthyl, 5-membered monocyclic oxa- or thia-aryl, 6-membered monocyclic aza- or diaza-aryl or optionally partially hydrogenated heteroaryl radical consisting of a 5- or 6-membered mono- or diaza- or oxa-heteroaryl radical and a 6-membered aryl radical, or when n is 1, X_2 is unsubstituted or lower alkyl- or cycloalkyl-substituted imino and X_3 is lower alkylene, R_3 is lower alkyl, carboxy, lower alkoxycarbonyl or carbamoyl,

R_4 is hydrogen, lower alkyl or phenyl that is unsubstituted or substituted by lower alkyl, lower alkoxy, phenoxy, halogen, carboxy, lower alkoxycarbonyl, carbamoyl, cyano, nitro and/or by trifluoromethyl,

X is oxy or thio,

X_1 is methylene, ethylene, a carbonyl group that is free or ketalised by a lower alkanol or by a lower alkanediol, a hydroxymethylene group that is free or etherified by a lower alkanol, or is a direct bond;

X_2 is a lower alkylene radical, an imino group that is unsubstituted or substituted by lower alkyl or by 5- to 7-membered cycloalkyl, or is a direct bond;

X_3 is lower alkylene or a direct bond;

X_4 is oxo or thioxo, and

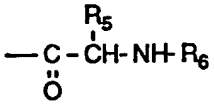
n is 1 or, when X_2 is lower alkylene and X_3 is a direct bond, n is 0,

and to the salts thereof.

The invention relates more especially, for example, to compounds of formula I wherein

R_1 is a phenyl-, diphenyl-, naphthyl- or fluorenyl-lower alkyl radical that is unsubstituted or substituted in the phenyl moiety by lower alkyl, lower alkoxy, di-lower alkylamino, halogen and/or by trifluoromethyl; a phenoxy-lower alkyl radical that is unsubstituted or substituted in the phenyl moiety by halogen and/or by triazolyl; a heteroaryl-lower alkyl radical containing as heteroaryl radical 6-membered monocyclic azaheteroaryl or bicyclic azaheteroaryl consisting of a 6-membered and a 5- or 6-membered ring; a benzoyl, naphthoyl, fluorenoyl or 3- to 8-membered cycloalkylcarbonyl radical that is unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, di-lower alkylamino, halogen, cyano and/or by trifluoromethyl; a phenyl- or diphenyl-lower alkanoyl radical that is unsubstituted or substituted in the phenyl moiety by lower alkyl, lower alkoxy, di-lower alkylamino, halogen and/or by trifluoromethyl; a heteroaryl-lower alkanoyl radical containing as heteroaryl radical 6-membered monocyclic azaheteroaryl or bi- or tri-cyclic azaheteroaryl consisting of a 6-membered and one or two 5- or 6-membered ring(s); a phenyl-lower alkoxycarbonyl or N-phenylcarbamoyl

radical that is unsubstituted or substituted in the phenyl moiety by lower alkyl, lower alkoxy, di-lower alkylamino, halogen and/or by trifluoromethyl; or a group of formula Ia



(Ia)

wherein

R_5 is hydrogen, or C_1-C_4alkyl that is unsubstituted or substituted by hydroxy, mercapto, amino, unsubstituted or hydroxy-substituted phenyl, carboxy, carbamoyl or by ureido, and

R_6 is C_2-C_7alkanoyl,

R_2 is 5- to 7-membered cycloalkyl, or a phenyl, naphthyl or 6-membered monocyclic azaheteroaryl radical that is unsubstituted or substituted by aromatically bonded lower alkyl, lower alkoxy, halogen, cyano, nitro and/or by trifluoromethyl,

R_3 is a phenyl, naphthyl or pyridyl radical that is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen and/or by trifluoromethyl, or a heteroaryl radical, consisting of an optionally partially hydrogenated 5- or 6-membered mono- or diaza- or oxa-heteroaryl radical and a 6-membered aryl radical, that is unsubstituted or C-substituted by lower alkyl, lower alkoxy, halogen and/or by trifluoromethyl and, as the case may be, N-substituted by lower alkanoyl,

R_4 is hydrogen or lower alkyl,

X is oxy or thio,

X_1 is methylene, ethylene, a carbonyl group that is free or ketalised by a lower alkanol or by a lower alkanediol, a hydroxymethylene group that is free or etherified by a lower alkanol, or is a direct bond,

X_2 is a lower alkylene radical, an imino group that is unsubstituted or substituted by lower alkyl or by 5- to 7-membered cycloalkyl, or is a direct bond,

X_3 is a direct bond,

X_4 is oxo, and

n is 1 or, when X_2 is a lower alkylene radical, n is 0,

and to the salts thereof.

The invention relates especially to compounds of formula I wherein

R_1 is benzoyl that is unsubstituted or substituted by C_1-C_4alkyl, C_1-C_4alkoxy, di-C_1-C_4alkylamino, halogen and/or by trifluoromethyl, such as benzoyl, 3-C_1-C_4alkyl-, 3-C_1-C_4alkoxy-, 3-halo-, 3-dimethylamino-, 3,5-di-C_1-C_4alkyl-, 3,5-di-C_1-C_4alkoxy-,

3,5-dihalo- or 3,5-ditrifluoromethyl-benzoyl, or is unsubstituted naphthoyl,

R_2 is phenyl that is unsubstituted or substituted by C_1-C_4alkyl, C_1-C_4alkoxy, halogen, cyano, nitro, carboxy, carbamoyl and/or by trifluoromethyl,

R_3 is phenyl or naphthyl that is unsubstituted or substituted by C_1-C_4alkyl, C_1-C_4alkoxy, phenoxy, halogen, carboxy, C_1-C_4alkoxycarbonyl, carbamoyl, cyano and/or by trifluoromethyl, or is unsubstituted pyridyl, benzofuranyl, unsubstituted or C_1-C_4alkyl-N-substituted indolyl or 2,3-dihydroindolyl, benzimidazolyl, quinolyl or 1,2,3,4-tetrahydroquinolinyl, or, when n is 1, X_2 is imino that is unsubstituted or substituted by C_1-C_4alkyl and X_3 is C_1-C_4alkylene, R_3 is C_1-C_7alkyl, carboxy, C_1-C_4alkoxycarbonyl or carbamoyl,

R_4 is hydrogen or C_1-C_4alkyl,

X is oxy or thio,

X_1 is methylene,

X_2 is C_1-C_4alkylene, imino, C_1-C_4alkylimino or a direct bond,

X_3 is C_1-C_4alkylene or a direct bond,

X_4 is oxo or thioxo, and

n is 1 or, when X_2 is C_1-C_4alkylene and X_3 is a direct bond, n is 0,

and to the salts thereof.

The invention relates very especially to compounds of formula I wherein

R_1 is benzoyl that is unsubstituted or substituted by C_1-C_4alkyl, C_1-C_4alkoxy, di-C_1-C_4alkylamino, halogen and/or by trifluoromethyl, such as benzoyl, 3-C_1-C_4alkyl-, 3-C_1-C_4alkoxy-, 3-halo-, 3-dimethylamino-, 3,5-di-C_1-C_4alkyl-, 3,5-di-C_1-C_4alkoxy-, 3,5-dihalo- or 3,5-ditrifluoromethyl-benzoyl,

R_2 is phenyl that is unsubstituted or substituted by C_1-C_4alkyl, such as methyl, C_1-C_4alkoxy, such as methoxy, halogen, such as chlorine, cyano, nitro, carboxy, carbamoyl and/or by trifluoromethyl,

R_3 is indolyl that is unsubstituted or N-substituted by C_1-C_4alkyl, such as methyl, or is unsubstituted quinolyl or 1,2,3,4-tetrahydroquinolinyl,

R_4 is hydrogen,

X is oxy,

X_1 is methylene,

X_2 is C_1-C_4alkylene, such as methylene, imino or a direct bond,

X_3 is methylene or a direct bond,

X_4 is oxo or thioxo, and

n is 1 or, when X_2 is C_1-C_4alkylene and X_3 is a direct bond, n is 0,

and to the salts thereof.

The invention relates above all, for example, to compounds of formula I wherein

R_1 is benzoyl that is unsubstituted or substituted by C_1-C_4alkyl, C_1-C_4alkoxy, di-C_1-C_4alkylamino, halogen and/or by trifluoromethyl, such as benzoyl, 3-C_1-C_4alkyl-, 3-C_1-C_4alkoxy-, 3-halo-, 3-dimethylamino-, 3,5-di-C_1-C_4alkyl-, 3,5-di-C_1-C_4alkoxy-, 3,5-dihalo- or 3,5-ditrifluoromethyl-benzoyl,

R_2 is phenyl that is unsubstituted or substituted by C_1-C_4alkyl, such as methyl, C_1-C_4alkoxy, such as methoxy, halogen, such as chlorine, cyano, nitro and/or by trifluoromethyl,

R_3 is unsubstituted quinolyl or 1,2,3,4-tetrahydroquinolinyl,

R_4 is hydrogen,

X is oxy or thio,

X_1 is methylene,

X_2 is C_1-C_4alkylene, such as methylene, imino or a direct bond,

X_3 is a direct bond,

X_4 is oxo, and

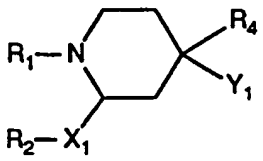
n is 1 or, when X_2 is C_1-C_4alkylene, n is 0,

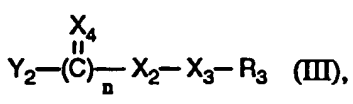
and to the salts thereof.

The invention relates specifically to the compounds of formula I mentioned in the Examples and to the salts thereof.

The invention relates further to a process, based on methods known *per se*, for the preparation of the compounds of the invention. That process comprises

a) condensing with one another compounds of formulae II and III



(II) and  (III),

wherein

R_1, R_2, R_3, R_4, X_1, X_2, X_3, X_4 and n are as defined and

one of the radicals Y_1 and Y_2 is hydroxy or mercapto, optionally in the form of a salt, and

the other is hydroxy or reactive esterified hydroxy or, when n is 1, etherified hydroxy, or wherein

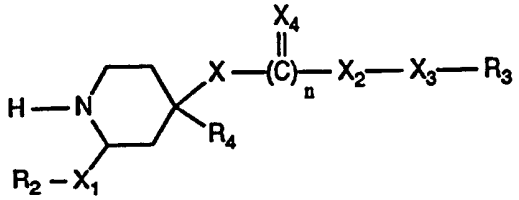
R_1, R_2, R_3, R_4, X_1, X_2, X_3 and X_4 are as defined,

Y_1 is hydroxy esterified by a carboxylic acid,

Y_2 is hydroxy that is free or etherified or in the form of a salt, and

n is 1, or

b) introducing the radical R_1 into a compound of formula IV



(IV),

wherein

R_2, R_3, R_4, X, X_1, X_2, X_3 and n are as defined,

and if desired, converting a resulting compound into a different compound of formula I, separating a mixture of isomers obtainable in accordance with the process into its components and isolating the preferred isomer, and/or converting a free compound obtainable in accordance with the process into a salt or converting a salt obtainable in accordance with the process into the corresponding free compound.

The reactions of the process and the preparation of novel starting materials and intermediates are carried out by analogy with the mode of reaction and formation of known starting materials and intermediates. In those reactions, even when not expressly mentioned below, the customary auxiliaries, such as catalysts, condensation and solvolysis agents and solvents and/or diluents, and the customary reaction conditions, such as temperature and pressure conditions, and, where appropriate, protective gases, are used.

In starting materials of formula II or III according to Process variant a), reactive esterified hydroxy is, for example, a halogen atom, such as a chlorine, bromine or iodine atom, or a sulfonyloxy group, for example methanesulfonyloxy or p-toluenesulfonyloxy, and, in the case of Y_2, if n is 1, a group of the formula -O-C(=X_4)-X_2-X_3-R_3.

There come into consideration as hydroxy Y_1 esterified by a carboxylic acid, for example, hydroxy or mercapto esterified by an aliphatic carboxylic acid, such as a lower alkanoic

acid, for example formic or acetic acid, an aromatic carboxylic acid, for example an unsubstituted or nitro-substituted benzoic acid, or a semiester of carbonic acid, for example an alkyl-, benzyl- or phenyl-monocarbonic acid ester.

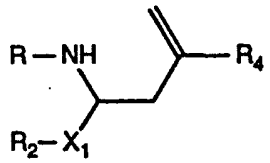
Etherified hydroxy groups are, for example, lower alkoxy, such as methoxy or ethoxy, or unsubstituted or substituted phenyloxy groups.

The reaction of compounds of formulae II and III is carried out in customary manner, for example in the presence of a condensation agent, such as a water-binding agent, or a basic condensation agent, or, starting from compounds of formulae II and III wherein Y_1 is hydroxy, n is 1 and Y_2 is etherified hydroxy, with removal of the liberated water, for example by azeotropic distillation, and in both cases advantageously in the presence of a solvent or diluent.

For example, the reaction of alcohols or mercaptans of formula II (Y_1 = hydroxy or mercapto) with acids or thioxo acids of formula III (Y_2 = hydroxy; n = 1) is carried out preferably in the presence of an acidic agent, such as a mineral acid, for example sulfuric acid, or in the presence of a water-binding agent, such as N,N-dicyclohexylcarbodiimide, while the reaction of alcohols and mercaptans of formula II (Y_1= hydroxy or mercapto) with reactive esters of formula III (Y_2= reactive esterified hydroxy; n = 0) or with acid halides and acid anhydrides of formula III (Y_2 = halogen or anhydridised hydroxy of the formula -O-C(=X_4)-X_2-X_3-R_3; n = 1) is carried out preferably in the presence of a basic condensation agent, such as an alkali metal hydroxide or carbonate, or a tertiary or sterically hindered secondary organic amine, such as a tri-lower alkylamine, for example triethylamine or diisopropylamine, or of an aromatic nitrogen base, for example pyridine.

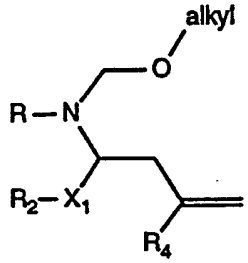
The reaction of alcohols and mercaptans of formula II (Y_1 = hydroxy or mercapto) with carboxylic acid esters of formula III (Y_2= etherified hydroxy or mercapto; n= 1) and the reaction of compounds of formula II (Y_1= hydroxy esterified by a carboxylic acid) with acids or esters of formula III (Y_2= free or etherified hydroxy or mercapto; n= 1) is carried out under customary transesterification conditions, for example in the presence of an acidic agent or of a basic condensation agent, such as one of those mentioned.

Starting materials of formula II wherein Y_1 is hydroxy, can be prepared, for example, by reacting a compound of formula IIa



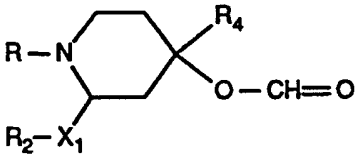
(IIa),

wherein R is a group R_1 or a customary amino-protecting group, such as carbobenzoxy, in customary manner, for example in the presence of benzyltributylammonium chloride in dichloromethane/sodium hydroxide solution, with a halomethyl alkyl ether, treating the resulting compound of formula IIb



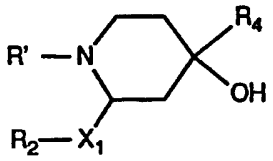
(IIb)

with an excess of formic acid, and hydrolysing the resulting compound of formula IIc



(IIc)

under acidic conditions, for example in the presence of concentrated hydrochloric acid, and condensing the resulting compound of formula IId



(IId),

wherein R' is a group R_1 or hydrogen, in customary manner, if necessary in a mixture of dichloromethane and aqueous sodium hydrogen carbonate solution, with a compound of the formula R_1-Y_3 (VI, Y_3= reactive esterified hydroxy) to form the corresponding compound of formula II (Y_1= hydroxy).

Further starting materials of formula II can be prepared from those starting materials as follows:

1) a compound of formula II wherein Y_1 is reactive esterified hydroxy can be prepared by reaction with an agent that introduces a reactive esterified hydroxy group, such as a sulfonic acid halide, for example methanesulfonic acid chloride, or a halogenating agent, such as thionyl chloride, preferably in the presence of pyridine;

2) compounds of formula II wherein Y_1 is hydroxy esterified by a carboxylic acid can be prepared by customary reaction with a reactive carboxylic acid derivative, such as a lower alkanoic acid halide or lower alkanoic acid anhydride.

Starting materials of formula III are known or can be prepared analogously to the formation of known starting materials of formula III.

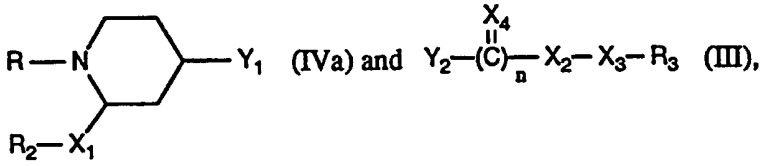
The introduction of the radical R_1 in accordance with Process variant b) is carried out in customary manner, for example by reaction with an agent that introduces the radical R_1, such as a compound of the formula R_1-Y_3 (VI), wherein R_1 has one of the meanings given above and Y_3 is reactive esterified hydroxy, or under reducing conditions with a compound of the formula R'_1=O (VII), wherein R'_1 is an unsubstituted or substituted aralkylidene, aryloxyalkylidene or heteroaralkylidene radical. Compounds of formula (VI) are, for example, N-acylating agents wherein in formula VI R_1 is an unsubstituted or substituted aroyl, heteroaroyl, cycloalkylcarbonyl, aralkanoyl, heteroarylalkanoyl or aryl-carbamoyl radical or the acyl radical of an optionally N-alkanoylated α-amino acid and Y_3 is free or etherified hydroxy, such as hydroxy, lower alkoxy or unsubstituted or substituted phenoxy, or reactive esterified hydroxy, such as halogen, especially chlorine, or a radical of the formula -O-R_1, or aralkylating, aryloxyalkylating or heteroarylalkylating agents of formula VI wherein R_1 is an unsubstituted or substituted aralkyl, aryloxyalkyl or hetero-aralkyl radical and Y_3 is reactive esterified hydroxy, such as halogen, for example chlorine, bromine or iodine, or a sulfonyloxy group, such as an alkanesulfonyloxy group or an unsubstituted or substituted benzenesulfonyloxy group, for example methane-, ethane-, benzene-, p-toluene- or p-bromobenzene-sulfonyloxy.

The reaction is carried out if necessary with the thermal decomposition of ammonium salts formed as intermediates or in the presence of a condensation agent, such as a water-binding agent, or a basic condensation agent, and in the presence of a solvent or diluent. For example, the reaction with acids of formula VI (Y_3= hydroxy) is carried out preferably in the presence of a water-binding agent, such as N,N-dicyclohexylcarbodiimide, or with thermal decomposition of the ammonium salt formed initially, while the reaction with acid

anhydrides of formula VI (Y_3= halogen or -O-(C=O)-R_1) and with aralkylating, aryloxy-alkylating or heteroarylalkylating agents of formula VI is carried out preferably in the presence of a basic condensation agent, such as an alkali metal hydroxide or carbonate, or of a teriary or sterically hindered secondary organic amine, such as a tri-lower alkylamine, for example triethylamine or diisopropylamine, or of an aromatic nitrogen base, for example pyridine.

The reaction with compounds of formula VII is carried out, for example, in the presence of hydrogen and a hydrogenation catalyst, such as a platinum or palladium catalyst, or Raney nickel, or in the presence of a di-light metal hydride, such as sodium borohydride or sodium cyanoborohydride, preferably in a solvent that is inert under the reaction conditions, such as a lower alkanol, such as methanol or ethanol, or a di-lower alkyl ether or lower alkylene ether, such as diethyl ether, dioxane or tetrahydrofuran.

The starting materials of formula IV can be prepared in customary manner, for example by reacting with one another compounds of formulae



(IVa) and

(III),

wherein R is an amino-protecting group, such as carbobenzoxy, for example as described above under Process variant a), and removing the amino-protecting group in customary manner.

Compounds obtainable according to the process can be converted in customary manner into different compounds of formula I.

For example, compounds of formula I wherein X_1 is carbonyl can be reduced in customary manner to the corresponding compounds of formula I wherein X_1 is hydroxymethylene, for example as described under Process variant b) or for the preparation of intermediates of formulae II and III. In an analogous manner it is also possible to reduce resulting compounds of formula I wherein X_1 is hydroxymethylene and/or n is 1 to the corresponding compounds of formula I wherein X_1 and/or n is 0, and X_2 is methylene or an alkylene radical lengthened by one methylene group.

In resulting compounds of formula I wherein X_1 is ketalised carbonyl, the carbonyl group can be freed in customary manner, for example by treatment with an acid. Conversely, carbonyl X_1 can be ketalised by reaction with a corresponding alcohol, such as a lower alkanol or a lower alkanediol.

Furthermore, in resulting compounds of formula I wherein X_2 is unsubstituted imino, a radical other than hydrogen can be introduced, for example by customary alkylation or cycloalkylation. Conversely, in resulting compounds of formula I wherein X_2 is imino substituted by alkyl, especially methyl, the alkyl group can be removed by treatment with a haloformic acid ester, such as formic acid methyl ester.

Resulting salts can be converted into the free compounds in a manner known *per se*, for example by treatment with a base, such as an alkali metal hydroxide, a metal carbonate or hydrogen carbonate, or ammonia, or another salt-forming base mentioned at the beginning, or with an acid, such as a mineral acid, for example with hydrogen chloride, or another salt-forming acid mentioned at the beginning.

Resulting salts can be converted into different salts in a manner known *per se*, for example by treatment with a suitable metal salt, such as a sodium, barium or silver salt, of a different acid in a suitable solvent in which an inorganic salt that forms is insoluble and is thus excluded from the reaction equilibrium, and base salts by freeing the free acid and converting it into a salt again.

The compounds of formula I, including their salts, may also be obtained in the form of hydrates or may include the solvent used for crystallisation.

In view of the close relationship between the novel compounds in free form and in the form of their salts, hereinbefore and hereinafter any reference to the free compounds or their salts should be understood as including the corresponding salts or free compounds, respectively, as appropriate and expedient.

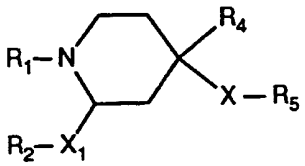
Resulting mixtures of diastereoisomers and mixtures of racemates can be separated in known manner into the pure diastereoisomers or racemates on the basis of the physicochemical differences between the constituents, for example by chromatography and/or fractional crystallisation.

Resulting racemates can also be separated into the optical antipodes by known methods, for example by recrystallisation from an optically active solvent, with the aid of micro-organisms or by reaction of the resulting diastereoisomeric mixture or racemate with an optically active auxiliary compound, for example according to the acidic, basic or functionally modifiable groups present in compounds of formula I with an optically active acid, base or an optically active alcohol, into mixtures of diastereoisomeric salts or functional derivatives, such as esters, and separation thereof into the diastereoisomers from which the desired enantiomer can be freed in customary manner. Examples of suitable bases, acids and alcohols are optically active alkaloid bases, such as strychnine, cinchonine or brucine, or D- or L-(1-phenyl)ethylamine, 3-pipecoline, ephedrine, amphetamine and similar synthetically obtainable bases, optically active carboxylic or sulfonic acids, such as quinic acid or D- or L-tartaric acid, D- or L-di-o-toluoyltartaric acid, D- or L-malic acid, D- or L-mandelic acid or D- or L-camphorsulfonic acid, or optically active alcohols, such as borneol or D- or L-(1-phenyl)ethanol.

The invention relates also to those forms of the process in which a compound obtainable as intermediate at any stage of the process is used as starting material and the remaining steps are carried out, or in which a starting material is used in the form of a salt or, especially, is formed under the reaction conditions.

The invention relates also to the novel starting materials developed specifically for the preparation of the compounds of the invention, especially to those starting materials resulting in the compounds of formula I described at the beginning as being preferred, to processes for the preparation thereof and to their use as intermediates.

The above applies preferably to compounds of formula V



(V),

wherein

R_5 is hydrogen, formyl or carbamoyl, and

R_1, R_2, R_4, X and X_1 are each as defined at the beginning for compounds of formula I.

Compounds of formula V wherein R_5 is hydrogen likewise have compound-P-antagonistic properties and can accordingly also be used as active ingredients of medicaments in pharmaceutical compositions for the treatment of the diseases mentioned at the beginning. Compounds of formula V wherein R_5 is formyl or carbamoyl are used preferably as intermediates in the preparation of active ingredients of medicaments, for example of formula I.

The invention accordingly relates also to compounds of formula V
wherein

R_1 is an unsubstituted or substituted aralkyl, aryloxyalkyl, heteroaralkyl, aroyl, heteroaroyl, cycloalkylcarbonyl, aralkanoyl, heteroarylalkanoyl, aralkoxycarbonyl or arylcarbamoyl radical, or the acyl radical of an α-amino acid that is unsubstituted or N-substituted by lower alkanoyl or by carbamoyl-lower alkanoyl,

R_2 is cycloalkyl or an unsubstituted or substituted aryl or heteroaryl radical,

R_4 is hydrogen or alkyl, and

R_5 is hydrogen, formyl or carbamoyl,

X is oxy or thio, and

X_1 is methylene, ethylene, a direct bond, a free or ketalised carbonyl group or a free or etherified hydroxymethylene group,

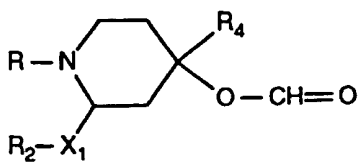
and to the salts thereof and to processes for the preparation thereof.

The invention relates preferably to those compounds of formula V wherein

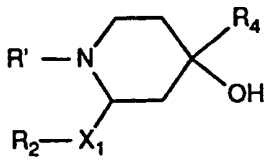
R_5 is hydrogen or formyl, and

R_1, R_2, R_4, X and X_1 are each as defined for the compounds of formula I described at the beginning as being preferred.

Compounds of formula V to which the invention relates include especially compounds of formulae IIc and IId



(IIc) and



(IId),

wherein

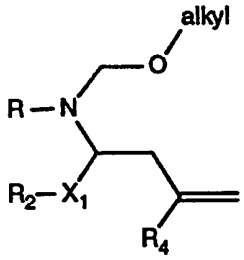
R and R' are each a group R_1, and

R_2, R_4 and X_1 are as defined for formula I,
and to corresponding 4-carbamoyloxypiperidine compounds.

Those compounds can also be represented by formula I shown at the beginning, wherein
n is 1,
X is oxy,
X_2 and X_3 are each a direct bond, and
R_4 is hydrogen.

Those compounds can also be represented by formula I shown at the beginning, wherein
n is 1,
X is oxy or thio,
X_2 and X_3 are each a direct bond, and
X and R_4 are as defined for formula I.

The invention relates further to a process, based on methods known *per se*, for the preparation of compounds of formula V wherein X is oxy. That process comprises subjecting a compound of formula IIb



(IIb),

wherein
alkyl is alkyl, especially lower alkyl, and R is a group R_1, and
R_1, R_2, R_4 and X_1 are each as defined for compounds of formula I, to intramolecular condensation, for example under acidic conditions, such as treatment with an excess of formic acid, and subjecting the resulting compound of formula V wherein R_5 is formyl to acid hydrolysis, for example in the presence of concentrated hydrochloric acid, to form the corresponding compound of formula V wherein R_5 is hydrogen.

Starting compounds of formula IIb can be obtained in the manner described under Process variant a) from corresponding compounds of formula IIa.

The novel compounds of formula I can be used, for example, in the form of pharmaceutical compositions that comprise a therapeutically effective amount of the active ingredient, optionally together with inorganic or organic, solid or liquid pharmaceutically acceptable carriers that are suitable for enteral, for example oral, or parenteral administration. There are used, for example, tablets or gelatin capsules that comprise the active ingredient together with diluents, for example lactose, dextrose, saccharose, mannitol, sorbitol, cellulose and/or lubricants, for example silica, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol. Tablets can also comprise binders, for example magnesium aluminium silicate, starches, such as corn, wheat, rice or arrowroot starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone, and, if desired, disintegrators, for example starches, agar, alginic acid or a salt thereof, for example sodium alginate, and/or effervescent mixtures, or absorbents, colouring agents, flavourings and sweeteners. The novel compounds of formula I can also be used in the form of parenterally administrable compositions or in the form of infusion solutions. Such solutions are preferably isotonic aqueous solutions or suspensions which, for example in the case of lyophilised compositions that comprise the active ingredient on its own or together with a carrier, for example mannitol, can be prepared before use. The pharmaceutical compositions may be sterilised and/or may comprise excipients, for example preservatives, stabilisers, wetting agents and/or emulsifiers, solubilisers, salts for regulating the osmotic pressure and/or buffers. The pharmaceutical compositions in question, which, if desired, may comprise further pharmacologically active substances, are prepared in a manner known *per se*, for example by means of conventional mixing, granulating, confectioning, dissolving or lyophilising processes, and comprise approximately from 0.1 % to 100 %, especially from approximately 1 % to approximately 50 %, in the case of lyophilisates up to approximately 100 %, active ingredient.

The present invention relates also to pharmaceutical compositions and medicaments comprising one of the compounds of formula I according to the invention or a pharmaceutically acceptable salt thereof. The pharmaceutical compositions according to the invention are especially pharmaceutical compositions intended for local administration, and especially for administration by inhalation, for example in the form of an aerosol, micronised powders or a finely sprayed solution, to mammals, especially humans, that comprise the active ingredient alone or together with a pharmaceutically acceptable carrier.

Pharmaceutical compositions for topical and local use are, for example for the treatment of the skin, lotions and creams which comprise a liquid or semi-solid oil-in-water or water-in-oil emulsion, and ointments (which preferably comprise a preservative). Suitable for the treatment of the eyes are eye drops which comprise the active ingredient in aqueous or oily solution, and eye ointments which are preferably manufactured in sterile form. Suitable for the treatment of the nose are aerosols and sprays (similar to those described below for the treatment of the respiratory tract), coarse powders which are administered by rapid inhalation through the nostrils, and especially nose drops which comprise the active ingredient in aqueous or oily solution; suitable for local treatment of the buccal cavity are lozenges which comprise the active ingredient in a mass generally formed of sugar and gum arabic or tragacanth, to which flavourings may be added, and pastilles which comprise the active ingredient in an inert mass, for example of gelatin and glycerol or sugar and gum arabic.

Pharmaceutical compositions suitable for administration in the form of aerosols or sprays are, for example, solutions, suspensions or emulsions of the compound of formula I according to the invention with a suitable pharmaceutically acceptable solvent, such as, especially, ethanol and water, or a mixture of such solvents. They may, as necessary, comprise other pharmaceutical excipients, such as non-ionic or anionic surface-active agents, emulsifiers and stabilisers, and also active ingredients of other kinds, and especially advantageously they can be mixed with a propellant gas, such as an inert gas under elevated pressure or especially with a readily volatile liquid, preferably a liquid that boils under normal atmospheric pressure below customary room temperature (for example from approximately -30 to +10°C), such as an at least partially fluorinated polyhalogenated lower alkane, or a mixture of such liquids. Such pharmaceutical compositions, which are used predominantly as intermediates or stock mixtures for the preparation of the corresponding medicaments in finished form, comprise the active ingredient customarily in a concentration of from approximately 0.1 to approximately 10 % by weight, especially from approximately 0.3 to approximately 3 % by weight. For the preparation of medicaments in finished form, such a pharmaceutical composition is introduced into suitable containers, such as flacons and pressurised bottles, which are provided with a spray device or valve suitable for such purposes. The valve is preferably constructed in the form of a metering valve which when operated releases a predetermined amount of liquid, corresponding to a predetermined dose of the active ingredient. In the preparation of the finished medicament form, it is also possible for appropriate amounts of the pharmaceutical composition present in stock solution form and of the propellant to be introduced

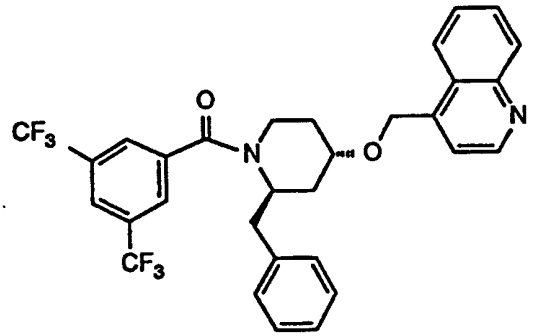
separately into the containers and to be mixed with one another only at that stage. The dose of the compound of formula I to be administered and the frequency of administration depend upon the effectiveness and the duration of efficacy of each individual compound, upon the severity of the disease to be treated and its symptoms, and upon the sex, age, weight and individual responsiveness of the mammal to be treated. On average, the recommended daily dose of a compound of formula I according to the invention for a mammal (especially a human) weighing 75 kg might be in the range of from approximately 10 to approximately 500, preferably from approximately 25 to approximately 250 mg, which can advantageously be administered in several doses per day, as necessary.

The invention relates also to the use of the compounds of formula I according to the invention in the alleviation or relief of pathological conditions and/or symptoms of the body of a mammal, especially of a human, that are attributable to the action of leucotrienes and that occur especially in the case of asthma. That use, and the corresponding method of treatment, comprises treating the affected body or body part with an antiallergically active amount of a compound of formula I on its own or in the form of a medicament, especially a pharmaceutical composition intended for inhalation. The expression "antiallergically effective amount" is to be understood as denoting an amount of active ingredient that is sufficient to ensure significant inhibition of the constriction caused by leucotrienes.

The invention relates further to the use of the compounds of formula I, preferably in the form of pharmaceutical compositions. The dose can depend upon various factors, such as the mode of administration, the species, age and/or individual condition. The daily doses to be administered are, in the case of oral administration, from approximately 0.25 to approximately 10 mg/kg, and, in the case of warm-blooded animals having a body weight of approximately 70 kg, they are preferably from approximately 20 mg to approximately 500 mg.

The following Examples illustrate the invention; temperatures are given in degrees Celsius and pressures in mbar.

Example 1: (2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-(4-quinolyl-methoxy)-piperidine



26 mg (1.08 mmol) of sodium hydride washed with hexane are added at room temperature to a solution of 117 mg (0.27 mmol) of (2R*,4S*)-2-benzyl-1-(3,5-bis(trifluoromethyl)-benzoyl)-4-hydroxy-piperidine in 1 ml of N,N-dimethylformamide. After 15 minutes, 99 mg (0.327 mmol) of 4-bromomethylquinoline are added to the clear solution and the mixture is heated to 80°. After 2 hours, water is added and extraction is carried out with methylene chloride. The organic phases are dried over sodium sulfate and concentrated using a rotary evaporator. The title compound crystallises from diethyl ether.
M.p.: 108-110°. TLC: methylene chloride/methanol/conc. ammonia (95:4.5:0.5) R_f= 0.48, FD-MS: M^+= 572.

The starting compound therefor is prepared as follows:

a) N-(1-benzyl-but-3-en-1-yl)-carbamic acid benzyl ester

5.3 g (31 mmol) of chloroformic acid benzyl ester are added dropwise in the course of 1 hour to a vigorously stirred and ice-cooled suspension of 5.0 g (31 mmol) of 1-benzyl-but-3-en-1-ylamine (McCarty, F.J.; Rosenstock, P.D.; Paolini, J.D.; Micucci, D.D.; Ashton, L.; Bennetts, W.W.; Palopoli, F.P., J. Med. Chem. 11, 534(1968)) in 20 ml of methylene chloride and 20 ml of 10 % aqueous sodium hydrogen carbonate solution in such a manner that the temperature does not rise above 8°. The reaction mixture is then stirred for a further 1 hour, the temperature rising to 16°. The phases are separated and the organic phase is washed once with 1N hydrochloric acid and once with saturated sodium chloride solution, dried over sodium sulfate and concentrated by evaporation using a rotary evaporator. 8.8 g (96 %) of a slightly coloured oil that solidifies when left to stand for a few days are obtained. The product is used further in the crude state, but can be

purified by crystallisation from toluene/hexane.
M.p.: 47-48°. TLC: hexane/ethyl acetate (3:1) R_f= 0.60.

b) N-(1-benzyl-but-3-en-1-yl)-N-ethoxymethyl-carbamic acid benzyl ester

3.515 g (37.2 mmol) of chloromethyl ethyl ether are added in small portions in the course of 2 hours to a vigorously stirred suspension, cooled to 5°, of 8.8 g (30 mmol) of N-(1-benzyl-but-3-en-1-yl)-carbamic acid benzyl ester and 0.193 g (0.62 mmol) of benzyl-tributylammonium chloride in 5 ml of methylene chloride and 20 ml of 50 % aqueous sodium hydroxide solution. The mixture is then stirred vigorously for 6 hours at from 5° to 10° to complete the reaction, and then diluted with water and methylene chloride. The phases are separated and the organic phase is washed with saturated sodium chloride solution, dried over sodium sulfate and concentrated using a rotary evaporator. 11 g of a liquid oil are obtained which are chromatographed on silica gel with ethyl acetate/hexane 1:10. 8.4 g (80 %) of the title compound are obtained. TLC: hexane/ethyl acetate (6:1) R_f=0.36.
^{1}H-NMR (200 MHz, chloroform): rotamer mixture, 7.45-7.02 (m, 10H), 5.87-5.60 (m, 1H), 5.25-4.92 (m, 4H), 4.88-4.37 (m, 2H), 4.17-3.95 (m, 1H), 3.55-2.85 (m, 4H), 2.85-2.25 (m, 2H), 1.20-1.00 (m, 3H).

c) (2R*,4S*)-2-benzyl-1-benzyloxycarbonyl-4-formyloxy-piperidine

8.4 g (23.7 mmol) of N-(1-benzyl-but-3-en-1-yl)-N-ethoxymethyl-carbamic acid benzyl ester are added dropwise in the course of 1 hour, at 5°, to 150 ml of 100 % formic acid. The reaction mixture is then stirred for 2 hours at 25° to complete the reaction. The reaction mixture is concentrated by evaporation using a rotary evaporator, and the residue is taken up in ethyl acetate, washed with aqueous sodium hydrogen carbonate solution, dried over sodium sulfate and concentrated by evaporation using a rotary evaporator. The product is chromatographed with ethyl acetate/hexane (1:3). The title compound (5.4 g, 64 %) is obtained in the form of a colourless oil. TLC: ethyl acetate/hexane (1:3) R_f= 0.30, FD-MS: M^+= 353.

d) (2R*,4S*)-2-benzyl-4-hydroxy-piperidine

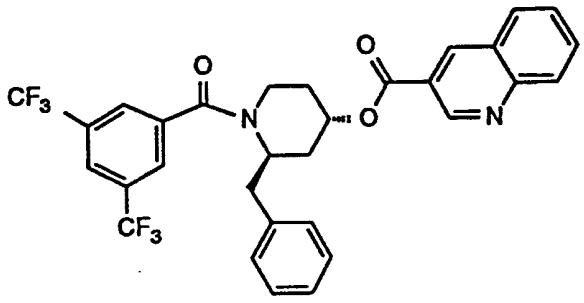
A suspension of 5.4 g (15.3 mmol) of (2R*,4S*)-2-benzyl-1-benzyloxycarbonyl-4-formyl-oxy-piperidine in 15 ml of 37 % hydrochloric acid is heated for 2 hours at 60°. The

slightly yellow reaction mixture is cooled and then rendered basic with 5N sodium hydroxide solution, saturated with sodium chloride and extracted twice with methylene chloride. The combined organic phases are dried over potassium carbonate and concentrated using a rotary evaporator. The title compound crystallises from ethyl acetate/methylene chloride (2.0 g, 68 %) in the form of white crystals. M.p.: 124-126°.
TLC: methylene chloride/methanol/conc. ammonia (180:19:1) R_f= 0.33, FD-MS: M^+=191.

e) (2R*,4S*)-2-benzyl-1-(3,5-bis(trifluoromethyl)benzoyl)-4-hydroxy-piperidine

2.16 g (7.8 mmol) of 3,5-bis(trifluoromethyl)benzoyl chloride are added dropwise in the course of 30 minutes to a vigorously stirred suspension, cooled to 5°, of 1.66 g (8.67 mmol) of (2R*,4S*)-2-benzyl-4-hydroxy-piperidine in 5 ml of methylene chloride and 10 ml of 10 % aqueous sodium hydrogen carbonate solution. The reaction is completed by stirring for 16 hours at room temperature. The phases are separated and the aqueous phase is extracted again with methylene chloride. The combined organic phases are washed with saturated sodium chloride solution, dried over sodium sulfate and concentrated using a rotary evaporator. The residue crystallises from ethyl acetate/hexane to yield the title compound (2.92 g, 78 %) in the form of white crystals.
M.p.: 93-96°, TLC: ethyl acetate/hexane (1:1) R_f= 0.3.

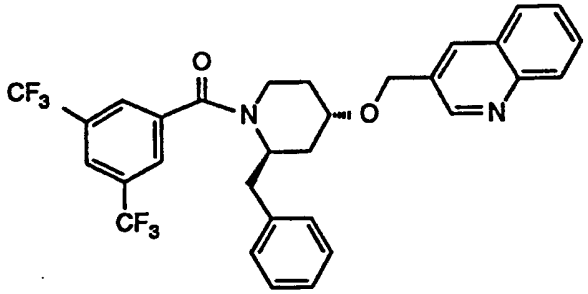
Example 2: (2R*,4S*)-quinoline-3-carboxylic acid [2-benzyl-1-(3,5-bistrifluoromethyl-benzoyl)-piperidin-4-yl] ester



At 0°, 100 mg (0.44 mmol) of quinoline-3-carboxylic acid chloride-hydrochloride are added to a solution of 147 mg (0.34 mmol) of (2R*,4S*)-2-benzyl-1-(3,5-bis(trifluoromethyl)benzoyl)-4-hydroxy-piperidine, 103 mg (1.02 mmol) of triethylamine and 9 mg (0.07 mmol) of N,N-dimethylaminopyridine in 2 ml of methylene chloride. After

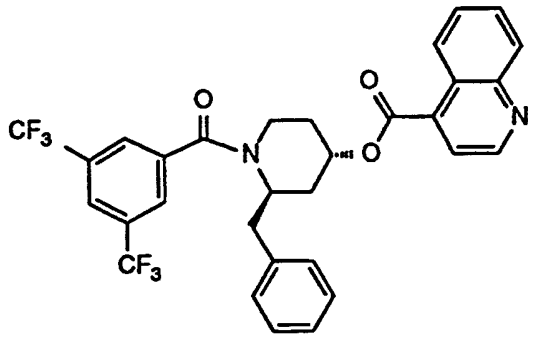
5 minutes the ice bath is removed and the reaction mixture is stirred for 2 hours at room temperature. The mixture is washed once with 10 % citric acid and once with saturated sodium chloride solution and the organic phases are dried over sodium sulfate and concentrated by evaporation using a rotary evaporator. The title compound crystallises from methylene chloride/diethyl ether in the form of white crystals. M.p.: 184°. TLC: methylene chloride/ethyl acetate (1:1) R_f= 0.64, FD-MS: M^+= 586.

Example 3: (2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-(3-quinolylmethoxy)-piperidine



Analogously to Example 1, 117 mg (0.27 mmol) of (2R*,4S*)- 2-benzyl-1-(3,5-bis(trifluoromethyl)benzoyl)-4-hydroxy-piperidine in 1 ml of N,N-dimethylformamide are reacted with 26 mg (1.08 mmol) of sodium hydride and 99 mg (0.327 mmol) of 3-bromomethylquinoline. The title compound crystallises from diethyl ether. M.p.: 157°. TLC: methylene chloride/methanol/conc. ammonia (190:9:1) R_f= 0.77, FD-MS: M^+= 572.

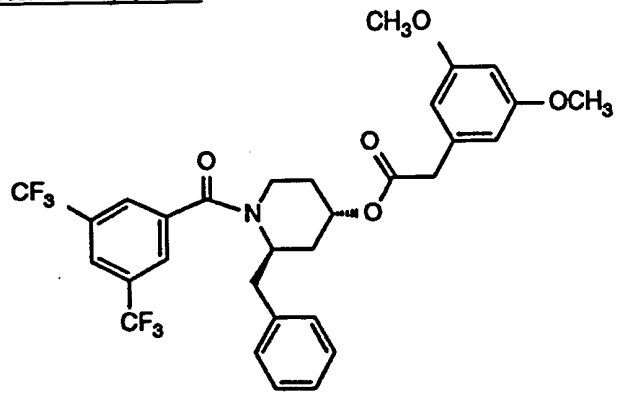
Example 4: (2R*,4S*)-quinoline-4-carboxylic acid [2-benzyl-1-(3,5-bis(trifluoromethyl)-benzoyl)-piperidin-4-yl] ester



Analogously to Example 2, 123 mg (0.28 mmol) of (2R*,4S*)-2-benzyl-1-(3,5-bis(tri-

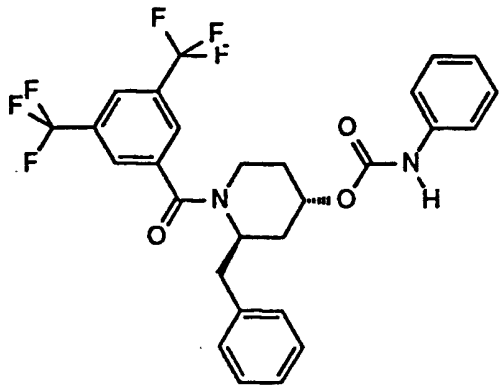
fluoromethyl)benzoyl)-4-hydroxy-piperidine, 86 mg (0.85 mmol) of triethylamine and 7 mg (0.06 mmol) of N,N-dimethylaminopyridine in 2 ml of methylene chloride are reacted with 84 mg (0.37 mmol) of quinoline-4-carboxylic acid chloride-hydrochloride. The crude product is chromatographed on silica gel with methylene chloride/ethyl acetate (4:1). The title compound is obtained in the form of a colourless foam. TLC: methylene chloride/ethyl acetate (4:1) R_f= 0.56, FD-MS: M^+= 586. $C_{31}H_{24}F_6N_2O_3$, calculated: C 63.48 %, H 4.12 %, N 4.78 %; found: C 63.32 %, H 4.23 %, N 4.67 %.

Example 5: (2R*,4S*)-3,5-dimethoxyphenylacetic acid [2-benzyl-1-(3,5-bis(trifluoro-methyl)benzoyl)-piperidin-4-yl] ester



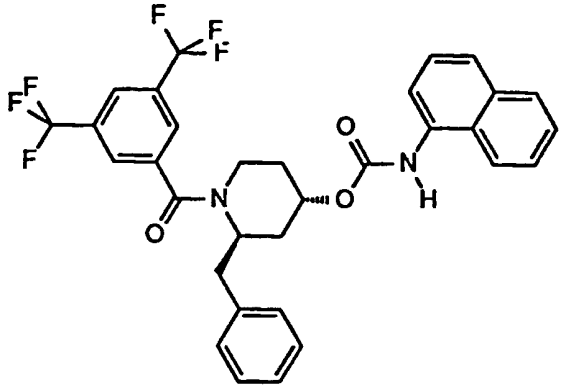
Analogously to Example 2, 147 mg (0.34 mmol) of (2R*,4S*)-2-benzyl-1-(3,5-bis(tri-fluoromethyl)benzoyl)-4-hydroxy-piperidine, 103 mg (1.02 mmol) of triethylamine and 9 mg (0.07 mmol) of N,N-dimethylaminopyridine in 2 ml of methylene chloride are reacted with 94 mg (0.44 mmol) of 3,5-dimethoxyphenylacetic acid chloride. The title compound is obtained in the form of an oil. TLC: methylene chloride/ethyl acetate (10:1) R_f= 0.63, DCI-MS: M^+= 609.

Example 6: (2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-(N-phenylcarbamoyloxy)-piperidine



149 mg (1.2 mmol) of phenyl isocyanate and 30 mg (0.25 mmol) of 4-dimethylamino-pyridine are added to a solution of 500 mg (1.2 mmol) of (2R*,4S*)-2-benzyl-1-(3,5-bis-(trifluoromethyl)benzoyl)-4-hydroxy-piperidine in 15 ml of toluene and the reaction mixture is stirred for 4 hours at 80°. The resulting solution is cooled to room temperature and taken up in ethyl acetate. The mixture is washed once with water and once with saturated sodium chloride solution, and the organic phases are dried over sodium sulfate and concentrated by evaporation using a rotary evaporator. The crude product is chromatographed on silica gel (toluene/ethyl acetate 95:5) and the title compound is obtained in the form of an oil.

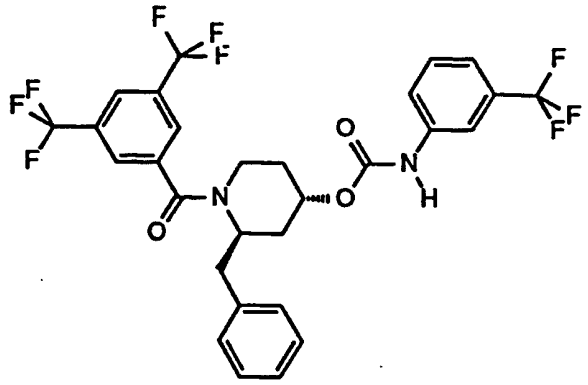
Example 7: (2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-[N-(1-naphthyl)carbamoyloxyl-piperidine



200 mg (1.2 mmol) of 1-naphthyl isocyanate and 30 mg (0.23 mmol) of 4-dimethyl-amino-pyridine are added to a solution of 500 mg (1.2 mmol) of (2R*,4S*)-2-benzyl-1-(3,5-bis(trifluoromethyl)benzoyl)-4-hydroxy-piperidine in 15 ml of toluene and the

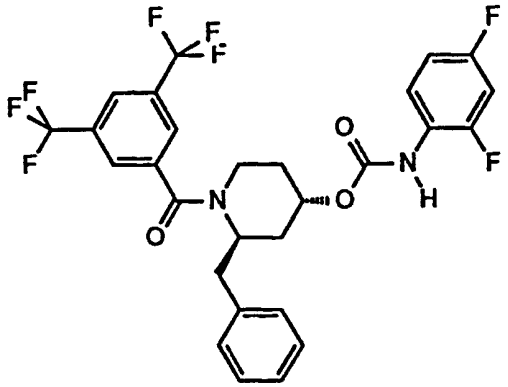
reaction mixture is stirred for 4 hours at 80°. The resulting solution is cooled to room temperature and taken up in ethyl acetate. The mixture is washed once with water and three times with saturated sodium chloride solution, and the organic phases are dried over sodium sulfate and concentrated by evaporation using a rotary evaporator. The crude product is chromatographed on silica gel (hexane/ethyl acetate 7:3). The title compound is obtained in the form of crystals. M.p.: 90-100°.

Example 8: (2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-[N-(3-trifluoro-methylphenyl)carbamoyloxy]-piperidine



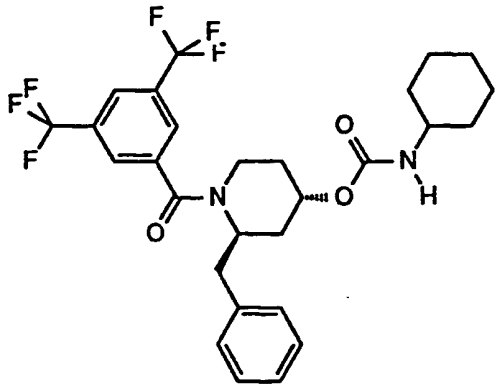
220 mg (1.2 mmol) of 3-trifluoromethylphenyl isocyanate and 30 mg (0.23 mmol) of 4-dimethylamino-pyridine are added to a solution of 500 mg (1.2 mmol) of (2R*,4S*)-2-benzyl-1-(3,5-bis(trifluoromethyl)benzoyl)-4-hydroxy-piperidine in 15 ml of toluene and the reaction mixture is stirred for 4.5 hours at 80°. The resulting solution is cooled to room temperature and taken up in ethyl acetate. The mixture is washed once with water and once with sodium chloride solution, and the organic phases are dried over sodium sulfate and concentrated by evaporation using a rotary evaporator. The crude product is chromatographed on silica gel (hexane/ethyl acetate 7:3). The title compound is obtained in the form of crystals. M.p.: 80-90°.

Example 9: (2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-[N-(2,4-difluoro-difluorophenyl)carbamoyloxy]-piperidine



290 mg (1.2 mmol) of 2,4-difluorophenyl isocyanate and 30 mg (0.23 mmol) of 4-dimethylamino-pyridine are added to a solution of 500 mg (1.2 mmol) of (2R*,4S*)-2-benzyl-1-(3,5-bis(trifluoromethyl)benzoyl)-4-hydroxy-piperidine in 15 ml of toluene and the reaction mixture is stirred for 4 hours at 80°. The resulting solution is cooled to room temperature and taken up in ethyl acetate. The mixture is washed once with water and once with saturated sodium chloride solution, and the organic phases are dried over sodium sulfate and concentrated by evaporation using a rotary evaporator. The crude product is chromatographed on silica gel (hexane/ethyl acetate 9:1). The title compound is obtained in the form of crystals. M.p.: 80-90°.

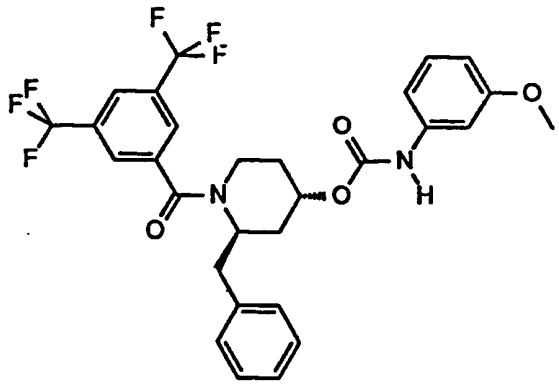
Example 10: (2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-(N-cyclohexylcarb-amoyloxy)-piperidine



150 mg (1.2 mmol) of cyclohexyl isocyanate and 90 mg (0.69 mmol) of 4-dimethyl-amino-pyridine are added to a solution of 500 mg (1.2 mmol) of (2R*,4S*)-2-benzyl-

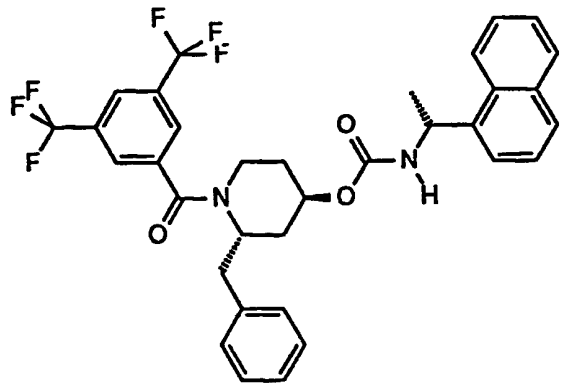
1-(3,5-bis(trifluoromethyl)benzoyl)-4-hydroxy-piperidine in 15 ml of toluene and the reaction mixture is stirred for 26 hours at 80°. The resulting solution is cooled to room temperature and taken up in ethyl acetate. The mixture is washed once with water and once with saturated sodium chloride solution, and the organic phases are dried over sodium sulfate and concentrated by evaporation using a rotary evaporator. The crude product is chromatographed on silica gel (hexane/ethyl acetate 7:3). The title compound is obtained in the form of crystals. M.p.: 65-68°.

Example 11: (2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-[N-(3-methoxy)-phenyl)carbamoyloxyl-piperidine



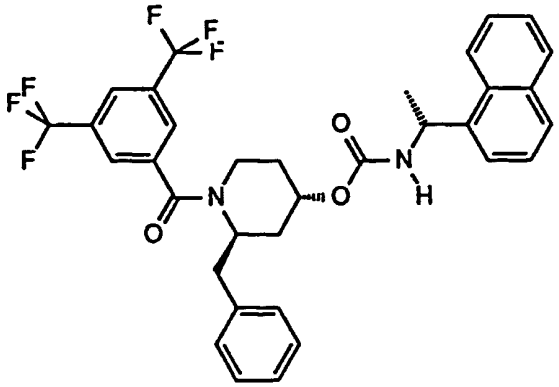
90 mg (0.6 mmol) of 3-methoxyphenyl isocyanate and 15 mg (0.12 mmol) of 4-dimethyl-amino-pyridine are added to a solution of 250 mg (0.6 mmol) of (2R*,4S*)-2-benzyl-1-(3,5-bis(trifluoromethyl)benzoyl)-4-hydroxy-piperidine in 10 ml of toluene and the reaction mixture is stirred for 5 hours at 80°. The resulting solution is cooled to room temperature and taken up in ethyl acetate. The mixture is washed once with water and once with saturated sodium chloride solution, and the organic phases are dried over sodium sulfate and concentrated by evaporation using a rotary evaporator. The crude product is chromatographed on silica gel (hexane/ethyl acetate 4:1). The title compound is obtained in the form of crystals. M.p.: 140-142°.

Example 12: (2S*,4R*,1'R)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-{N-[2-(1-naphthyl)ethyl]carbamoyloxy}-piperidine



230 mg (1.2 mmol) of (R)-1-naphthyl-ethyl isocyanate and 30 mg (0.23 mmol) of 4-dimethylamino-pyridine are added to a solution of 500 mg (1.2 mmol) of (2R*,4S*)-2-benzyl-1-(3,5-bis(trifluoromethyl)benzoyl)-4-hydroxy-piperidine in 15 ml of toluene and the reaction mixture is stirred for 24 hours at 80°. The resulting solution is cooled to room temperature and taken up in ethyl acetate. The mixture is washed once with water and once with saturated sodium chloride solution, and the organic phases are dried over sodium sulfate and concentrated by evaporation using a rotary evaporator. The crude product is chromatographed on silica gel (toluene/ethyl acetate 98:2). The title compound is obtained in the form of crystals. M.p.: 85-90°.

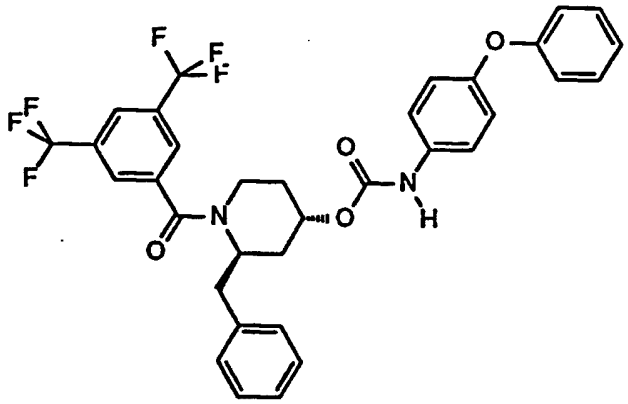
Example 13: (2R*,4S*,1'R)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-{N-[2-(1-naphthyl)ethyl]carbamoyloxy}-piperidine



230 mg (1.2 mmol) of (R)-1-naphthyl-ethyl isocyanate and 30 mg (0.23 mmol) of 4-dimethylamino-pyridine are added to a solution of 500 mg (1.2 mmol) of (2R*,4S*)-

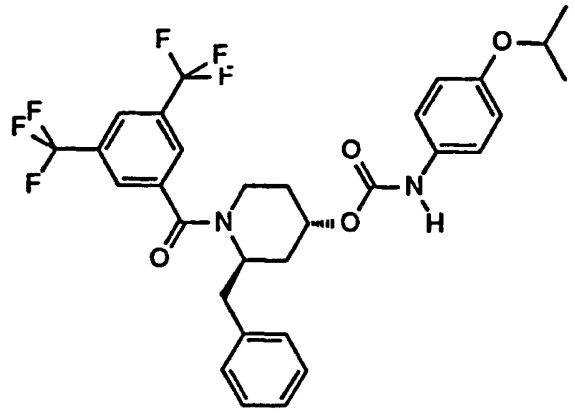
2-benzyl-1-(3,5-bis(trifluoromethyl)benzoyl)-4-hydroxy-piperidine in 15 ml of toluene and the reaction mixture is stirred for 24 hours at 80°. The resulting solution is cooled to room temperature and taken up in ethyl acetate. The mixture is washed once with water and once with saturated sodium chloride solution, and the organic phases are dried over sodium sulfate and concentrated by evaporation using a rotary evaporator. The crude product is chromatographed on silica gel (toluene/ethyl acetate 98:2). The title compound is obtained in the form of crystals. M.p.: 85-90°.

Example 14: (2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-[N-(4-phenoxy)-phenyl)carbamoyloxy]-piperidine



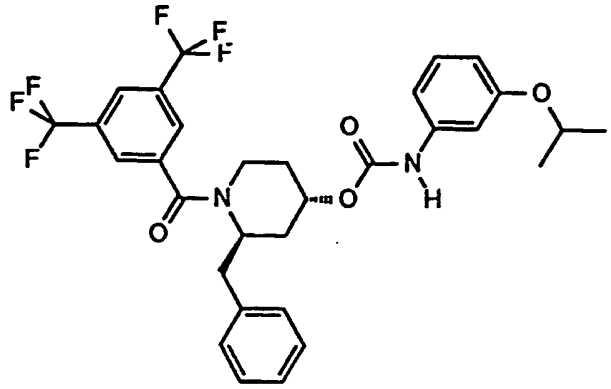
250 mg (1.2 mmol) of 4-phenoxyphenyl isocyanate and 30 mg (0.23 mmol) of 4-dimethyl-amino-pyridine are added to a solution of 500 mg (1.2 mmol) of (2R*,4S*)-2-benzyl-1-(3,5-bis(trifluoromethyl)benzoyl)-4-hydroxy-piperidine in 15 ml of toluene and the reaction mixture is stirred for 4 hours at 80°. The resulting solution is cooled to room temperature and taken up in ethyl acetate. The mixture is washed once with water and once with saturated sodium chloride solution, and the organic phases are dried over sodium sulfate and concentrated by evaporation using a rotary evaporator. The crude product is chromatographed on silica gel (hexane/ethyl acetate 7:3) and the title compound is obtained in the form of a foam.

Example 15: (2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-[N-(4-isopropyl-oxy)phenyl)carbamoyloxyl-piperidine



500 mg (2.8 mmol) of 4-isopropoxyphenyl isocyanate and 30 mg (1.2 mmol) of 4-dimethylamino-pyridine are added to a solution of 500 mg (1.2 mmol) of (2R*,4S*)-2-benzyl-1-(3,5-bis(trifluoromethyl)benzoyl)-4-hydroxy-piperidine in 20 ml toluene and the reaction mixture is stirred for 4 hours at 80°. The resulting solution is cooled to room temperature and taken up in ethyl acetate. The mixture is washed once with water and once with saturated sodium chloride solution, and the organic phases are dried over sodium sulfate and concentrated by evaporation using a rotary evaporator. The crude product is chromatographed on silica gel (hexane/ethyl acetate 9:1). The title compound is obtained in the form of crystals. M.p.: 80-87°.

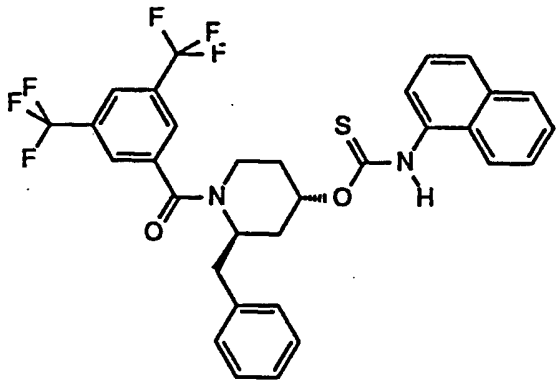
Example 16: (2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-[N-(3-isopropyl-oxy-phenyl)carbamoyloxyl-piperidine



500 mg (2.8 mmol) of 3-isopropoxyphenyl isocyanate and 30 mg (1.2 mmol) of 4-di-

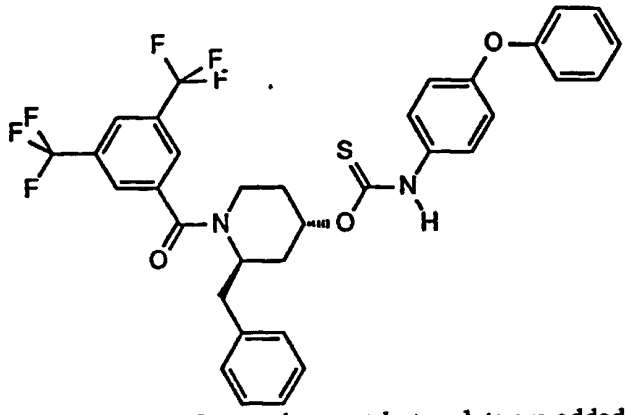
methylamino-pyridine are added to a solution of 500 mg (1.2 mmol) of (2R*,4S*)-2-benzyl-1-(3,5-bis(trifluoromethyl)benzoyl)-4-hydroxy-piperidine in 15 ml of toluene and the reaction mixture is stirred for 4 hours at 80°. The resulting solution is cooled to room temperature and taken up in ethyl acetate. The mixture is washed once with water and once with saturated sodium chloride solution, and the organic phases are dried over sodium sulfate and concentrated by evaporation using a rotary evaporator. The crude product is chromatographed on silica gel (hexane/ethyl acetate 4:1). The title compound is obtained in the form of crystals. M.p.: 137-140°.

Example 17: (2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-[N-(1-naphthyl)-thiocarbamoyloxy]-piperidine



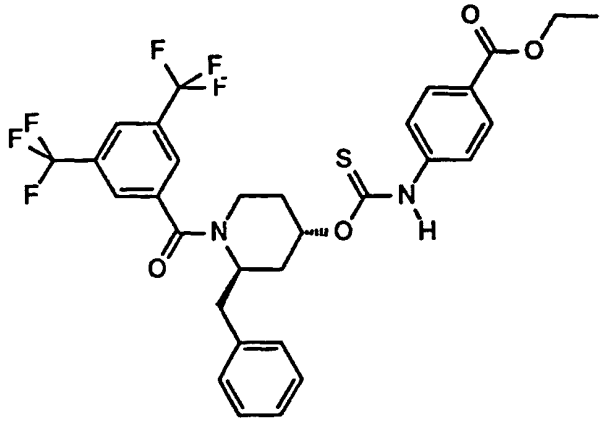
Under argon, 135 mg (1.2 mmol) of potassium tert-butanolate are added to a solution of 500 mg (1.2 mmol) of (2R*,4S*)-2-benzyl-1-(3,5-bis(trifluoromethyl)benzoyl)-4-hydroxy-piperidine in 10 ml of toluene. The resulting yellowish solution is stirred for 30 minutes at room temperature and then 220 mg (1.2 mmol) of 1-naphthyl isothiocyanate are added thereto. After 2 hours, 10 ml of water are added dropwise to the reaction solution which is then rendered acidic with 2 ml of 1N hydrochloric acid solution. Ethyl acetate is added and the organic phase is then washed once with water and twice with saturated sodium chloride solution, dried over sodium sulfate and concentrated by evaporation using a rotary evaporator. The crude product is chromatographed on silica gel (hexane/ethyl acetate 4:1). The title compound is obtained in the form of crystals. M.p.: 164-167°.

Example 18: (2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-[N-(4-phenoxy-phenyl)thiocarbamoyloxyl-piperidine



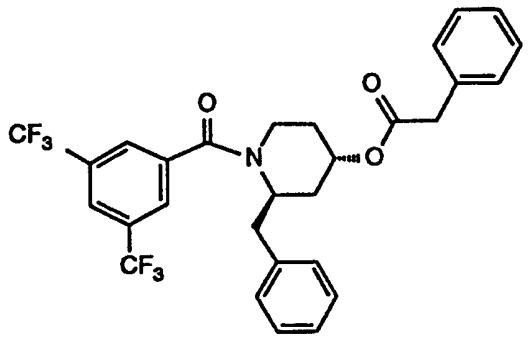
Under argon, 140 mg (1.2 mmol) of potassium tert-butanolate are added to a solution of 500 mg (1.2 mmol) of (2R*,4S*)-2-benzyl-1-(3,5-bis(trifluoromethyl)benzoyl)-4-hydroxy-piperidine in 10 ml of toluene. The resulting yellowish solution is stirred for 30 minutes at room temperature and then 270 mg (1.2 mmol) of 4-phenoxy-phenyl isothiocyanate are added thereto. After 3 hours, the reaction solution is taken up in ethyl acetate and extracted once with 0.1N hydrochloric acid solution and once with water, and then washed twice with saturated sodium chloride solution, dried over sodium sulfate and concentrated by evaporation using a rotary evaporator. The crude product is chromatographed on silica gel (hexane/ethyl acetate 4:1). The title compound is obtained in the form of crystals. M.p.: 174-177°.

Example 19: (2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-[N-(4-ethoxy-carbonylphenyl)thiocarbamoyloxyl-piperidine



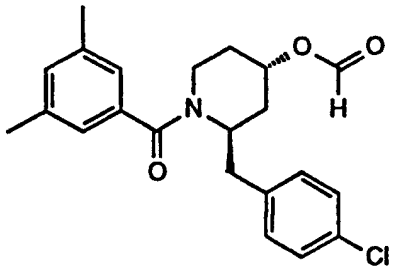
Under argon, 135 mg (1.2 mmol) of potassium tert-butanolate are added to a solution of 500 mg (1.2 mmol) of (2R*,4S*)-2-benzyl-1-(3,5-bis(trifluoromethyl)benzoyl)-4-hydroxy-piperidine in 10 ml of toluene. The resulting yellowish solution is stirred for 30 minutes at room temperature and then 250 mg (1.2 mmol) of 4-ethoxycarbonyl-phenyl isothiocyanate are added thereto. After 3 hours, the reaction solution is taken up in ethyl acetate and extracted once with 0.1N hydrochloric acid solution and once with water, and then washed twice with saturated sodium chloride solution, dried over sodium sulfate and concentrated by evaporation using a rotary evaporator. The crude product is chromatographed on silica gel (hexane/ethyl acetate 4:1). The title compound is obtained in the form of crystals. M.p.: 212-215°.

Example 20: (2R*,4S*)-phenylacetic acid [2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-piperidin-4-yl] ester



Analogously to Example 2, 149 mg (0.34 mmol) of (2R*,4S*)-2-benzyl-1-(3,5-bis(trifluoromethyl)benzoyl)-4-hydroxy-piperidine, 105 mg (1.04 mmol) of triethylamine and 9 mg (0.07 mmol) of N,N-dimethylaminopyridine in 2 ml of methylene chloride are reacted with 64 mg (0.42 mmol) of phenylacetic acid chloride. The title compound is obtained in the form of an oil. TLC: toluene/ethyl acetate (10:1) R_f= 0.2, FD-MS: M^+= 549.

Example 21: (2R*,4S*)-2-(4-chlorobenzyl)-1-(3,5-dimethylbenzoyl)-4-formyloxy-piperidine



N-[1-(4-Chloro-benzyl)-but-3-enyl]-N-ethoxyethyl-3,5-dimethyl-benzamide (680 mg, 1.76 mmol) is stirred for 90 minutes at 0-5° in 10 ml of formic acid. The mixture is concentrated by evaporation under reduced pressure, and the residue is then taken up in dichloromethane and saturated $NaHCO_3$ solution. The organic phase is separated off, then washed with saturated sodium chloride solution, dried over Na_2SO_4 and concentrated by evaporation under reduced pressure. Chromatography on silica gel with ethyl acetate/-hexane (1:4) as eluant yields 160 mg (23 %) of the title compound in the form of a colourless oil; TLC (ethyl acetate/hexane: 1:3): $R_f = 0.30$; MS: 385 (M^+).

The starting materials can be prepared as follows:

a) N-[1-(4-chlorobenzyl)-but-3-enyl]-3,5-dimethyl-benzamide

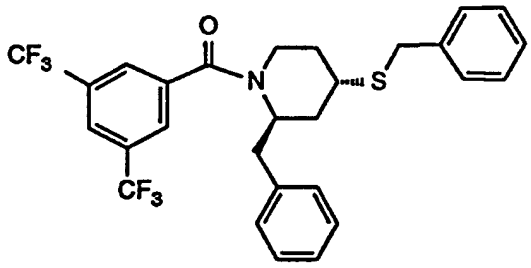
In the course of 2 hours, 4.3 g (25.6 mmol) of 3,5-dimethylbenzoyl chloride are added to a solution, stirred at 0°, of 5.0 g (25.6 mmol) of 1-(4-chloro)phenyl-pent-4-en-2-ylamine and 5.33 ml (38.4 mmol) of triethylamine in 100 ml of dichloromethane. The reaction mixture is then stirred for a further 1 hour, 1N hydrochloric acid is added thereto and extraction is carried out with dichloromethane. The organic phase is washed neutral with saturated sodium chloride solution, dried over sodium sulfate and concentrated by evaporation under reduced pressure. The crude product is crystallised from ethyl acetate/hexane and yields 7.36 g (88 %) of white crystals; m.p.: 116-118°; TLC (hexane/ethyl acetate; 3:1): $R_f = 0.37$

b) N-[1-(4-chlorobenzyl)-but-3-enyl]-N-ethoxyethyl-3,5-dimethyl-benzamide

In the course of 2 hours, at 0-5°, 2.36 ml (25.2 mmol) of chloromethyl ethyl ether are

added in small portions to a vigorously stirred solution of 5.5 g (16.8 mmol) of N-[1-(4-chlorobenzyl)-but-3-enyl]-3,5-dimethyl-benzamide and 100 mg of benzyltributyl-ammonium chloride in 15 ml of 50 % aqueous sodium hydroxide solution and 15 ml of dichloromethane. The organic phase is taken up in dichloromethane and water, and the organic phase is separated off, dried over sodium sulfate and concentrated to dryness by evaporation under reduced pressure. The oily residue is purified by chromatography on silica gel with ethyl acetate/hexane (1:4) as eluant and yields 2.42 g (37 %) of the title compound in the form of a colourless oil; TLC (ethyl acetate/hexane; 1:3): $R_f = 0.41$; ^{1}H-NMR (300 MHz, chloroform): mixture of rotamers, d = 7.31-7.18 (m, 4H), 7.04-6.85 (m, 2.6H), 6.42 (br, s, 0.4H), 5.92-5.60 (m, 1H), 5.20-5.02 (m, 2H), 4.54-4.24 (m, 2H), 3.96-3.67 (m, 1H), 3.25-2.40 (m, 6H), 2.28 (s, approx. 5H), 2.24 (s, approx. 1H), 1.34-1.21 (m, approx. 0.5H), 1.08 (t, J = 7, approx. 2.5H).

Example 22: (2R*,4S*)-[2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-piperidin-4-yl] thio-ether



85 mg (1.96 mmol) of a 55 % suspension of sodium hydride in mineral oil are added to a solution of 607 mg (4.89 mmol) of benzylmercaptan in 5 ml of dimethyl sulfoxide. The reaction mixture is allowed to react for 15 minutes at room temperature and then, in the course of 2 hours, with stirring, a solution of 498 mg of 2-benzyl-1-(3,5-bistrifluoro-methylbenzoyl)-4-sulfonyloxy-piperidine in 2 ml of dimethyl sulfoxide is added dropwise thereto. The reaction mixture is then stirred for 1 hour at room temperature, and then concentrated by evaporation and chromatographed on silica gel with hexane/ethyl acetate (10:1) as eluant. The title compound is obtained in the form of an oil; TLC (hexane/ethyl acetate, 5:1) $R_f = 0.23$; FD-MS: $M^+ = 517$.

The starting material can be prepared, for example, as follows:

a) 2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-hydroxy-piperidine

Analogously to Example 1e), 280 mg (1.46 mmol) of 2-benzyl-piperidin-4-ol in 2 ml of methylene chloride and 4 ml of 10 % aqueous sodium hydrogen carbonate solution are reacted with 366 mg (1.33 mmol) of 3,5-bistrifluoromethylbenzoyl chloride. The title compound is obtained in the form of an oil.

b) 2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-sulfonyloxy-piperidine

While cooling with ice, 0.20 ml (2.6 mmol) of methanesulfonic acid chloride is added dropwise to a solution of 560 mg (1.30 mmol) of 2-benzyl-1-(3,5-bistrifluoromethyl-benzoyl)-piperidin-4-ol in 3 ml of pyridine. The reaction mixture is then stirred for 30 minutes at 0° and for 2 hours at room temperature, concentrated using a rotary evaporator and taken up in ethyl acetate. The title compound is obtained after washing with water and saturated sodium chloride solution, drying over magnesium sulfate and further concentration by evaporation using a rotary evaporator.

Example 23: In a manner analogous to that described in Examples 1 to 22 it is also possible to prepare:

(2R*,4S*)-2-(4-nitrobenzyl)-1-(3,5-dimethylbenzoyl)-4-formyloxy-piperidine;

(2R*,4S*)-2-(2,4-dichlorobenzyl)-1-(3,5-dimethylbenzoyl)-4-formyloxy-piperidine;

(2R*,4S*)-2-(3,4-dichlorobenzyl)-1-(3,5-dimethylbenzoyl)-4-formyloxy-piperidine;

(2R*,4S*)-2-(4-methoxybenzyl)-1-(3,5-dimethylbenzoyl)-4-formyloxy-piperidine;

(2R*,4S*)-2-(2,4-dimethoxybenzyl)-1-(3,5-dimethylbenzoyl)-4-formyloxy-piperidine;

(2R*,4S*)-2-(4-carboxybenzyl)-1-(3,5-dimethylbenzoyl)-4-formyloxy-piperidine;

(2R*,4S*)-2-(4-carboxamidobenzyl)-1-(3,5-dimethylbenzoyl)-4-formyloxy-piperidine;

(2R*,4S*)-2-(4-nitrobenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-formyloxy-piperidine;

(2R*,4S*)-2-(2,4-dichlorobenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-formyloxy-piperidine;

(2R*,4S*)-2-(3,4-dichlorobenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-formyloxy-piperidine;

(2R*,4S*)-2-(4-methoxybenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-formyloxy-piperidine;

(2R*,4S*)-2-(2,4-dimethoxybenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-formyloxy-piperidine;

(2R*,4S*)-2-(4-carboxybenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-formyloxy-piperidine;

(2R*,4S*)-2-(4-carboxamidobenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-formyloxy-piperidine;

(2R*,4S*)-2-(4-nitrobenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-(4-quinolinylmethoxy)-piperidine;

(2R*,4S*)-2-(2,4-dichlorobenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-(4-quinolinylmethoxy)-piperidine;

(2R*,4S*)-2-(3,4-dichlorobenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-(4-quinolinylmethoxy)-piperidine;

(2R*,4S*)-2-(4-methoxybenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-(4-quinolinylmethoxy)-piperidine;

(2R*,4S*)-2-(2,4-dimethoxybenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-(4-quinolinylmethoxy)-piperidine;

(2R*,4S*)-2-(4-carboxybenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-(4-quinolinylmethoxy)-piperidine;

(2R*,4S*)-2-(4-carboxamidobenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-(4-quinolinyl-methoxy)-piperidine;

(2R*,4S*)-2-(4-nitrobenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-(3-quinolinylmethoxy)-piperidine;

(2R*,4S*)-2-(2,4-dichlorobenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-(3-quinolinyl-methoxy)-piperidine;

(2R*,4S*)-2-(3,4-dichlorobenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-(3-quinolinyl-methoxy)-piperidine;

(2R*,4S*)-2-(4-methoxybenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-(3-quinolinyl-methoxy)-piperidine;

(2R*,4S*)-2-(2,4-dimethoxybenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-3-(3-quinolinyl-methoxy)-piperidine;

(2R*,4S*)-2-(4-carboxybenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-(3-quinolinyl-methoxy)-piperidine;

(2R*,4S*)-2-(4-carboxamidobenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-(3-quinolinyl-methoxy)-piperidine;

(2R*,4S*)-quinoline-3-carboxylic acid [2-(4-nitrobenzyl)-1-(3,5-bistrifluoromethyl-benzoyl)-piperidin-4-yl] ester;

(2R*,4S*)-quinoline-3-carboxylic acid [2-(2,4-dichlorobenzyl)-1-(3,5-bistrifluoromethyl-benzoyl)-piperidin-4-yl] ester;

(2R*,4S*)-quinoline-3-carboxylic acid [2-(3,4-dichlorobenzyl)-1-(3,5-bistrifluoromethyl-benzoyl)-piperidin-4-yl] ester;

(2R*,4S*)-quinoline-3-carboxylic acid [2-(4-methoxybenzyl)-1-(3,5-bistrifluoromethyl-benzoyl)-piperidin-4-yl] ester;

(2R*,4S*)-quinoline-3-carboxylic acid [2-(2,4-dimethoxybenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-piperidin-4-yl] ester;

(2R*,4S*)-quinoline-3-carboxylic acid [2-(4-carboxybenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-piperidin-4-yl] ester;

(2R*,4S*)-quinoline-3-carboxylic acid [2-(4-carboxamidobenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-piperidin-4-yl] ester;

(2R*,4S*)-quinoline-4-carboxylic acid [2-(4-nitrobenzyl)-1-(3,5-bistrifluoromethyl)-benzoyl)-piperidin-4-yl] ester;

(2R*,4S*)-quinoline-4-carboxylic acid [2-(2,4-dichlorobenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-piperidin-4-yl] ester;

(2R*,4S*)-quinoline-4-carboxylic acid [2-(3,4-dichlorobenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-piperidin-4-yl] ester;

(2R*,4S*)-quinoline-4-carboxylic acid [2-(4-methoxybenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-piperidin-4-yl] ester;

(2R*,4S*)-quinoline-4-carboxylic acid [2-(2,4-dimethoxybenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-piperidin-4-yl] ester;

(2R*,4S*)-quinoline-4-carboxylic acid [2-(4-carboxybenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-piperidin-4-yl] ester;

(2R*,4S*)-quinoline-4-carboxylic acid [2-(4-carboxamidobenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-piperidin-4-yl] ester;

(2R*,4S*)-1-methyl-2-indolecarboxylic acid [2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-piperidin-4-yl] ester;

(2R*,4S*)-3,5-dimethoxyphenylacetic acid [2-benzyl-1-(3,5-dimethylbenzoyl)-piperidin-4-yl] ester;

(2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-(N-benzylcarbamoyloxy)-piperidine;

(2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-[N-(3-cyanophenyl)carbamoyloxy]-piperidine;

(2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-(N-heptyl)carbamoyloxy)-piperidine;

(2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-(N-diisopropylcarbamoyloxy)-piperidine;

(2R*,4S*)-[2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-piperidin-4-yloxycarbonylamino]-acetic acid ethyl ester;

(2R*,4S*)-[2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-[N-ethoxycarbonylcarbamoyloxy]-piperidine;

(2R*,4S*)-[2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-[N-ethoxycarbonylthiocarbamoyloxy]-piperidine;

(2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-(4-quinolylmethylthio)-piperidine and

(2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-(3-quinolylmethylthio)-piperidine.

Example 23: Tablets, each comprising 50 mg of (2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-(3-quinolylmethoxy)-piperidine or a salt, for example the hydrochloride, thereof, can be prepared as follows:

Composition (10 000 tablets)

active ingredient	500.0 g
lactose	500.0 g

potato starch	352.0 g
gelatin	8.0 g
talc	60.0 g
magnesium stearate	10.0 g
silicon dioxide (highly dispersed)	20.0 g
ethanol	q.s.

The active ingredient is mixed with the lactose and 292 g of potato starch and the mixture is moistened with an ethanolic solution of the gelatin and granulated through a sieve. After drying, the remainder of the potato starch, the magnesium stearate, the talc and the silicon dioxide are added and the mixture is compressed to form tablets, each weighing 145.0 mg and containing 50.0 mg of active ingredient, which can, if desired, be provided with breaking notches for finer adaptation of the dose.

Example 24: Film-coated tablets, each comprising 100 mg of (2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-(3-quinolylmethoxy)-piperidine or a salt, for example the hydrochloride, thereof, can be prepared as follows:

Composition (for 1000 film-coated tablets)

active ingredient	100.0 g
lactose	100.0 g
maize starch	70.0 g
talc	8.5 g
calcium stearate	1.5 g
hydroxypropyl methylcellulose	2.36 g
shellac	0.64 g
water	q.s.
methylene chloride	q.s.

The active ingredient, the lactose and 40 g of the maize starch are mixed and moistened with a paste prepared from 15 g of maize starch and water (with heating) and granulated. The granules are dried and the remainder of the maize starch, the talc and the calcium stearate are added and mixed with the granules. The mixture is compressed to form tablets (weight: 280 mg) which are then coated with a solution of the hydroxypropyl methylcellulose and the shellac in methylene chloride; final weight of each film-coated tablet:

283 mg.

Example 25: Dry-filled gelatin capsules, each containing 100 mg of active ingredient, for example (2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-(3-quinolylmethoxy)-piperidine or a salt, for example the hydrochloride, thereof, can be prepared, for example, as follows:

Composition (for 1000 capsules)

active ingredient	100.0 g
lactose	250.0 g
microcrystalline cellulose	30.0 g
sodium lauryl sulfate	2.0 g
magnesium stearate	8.0 g

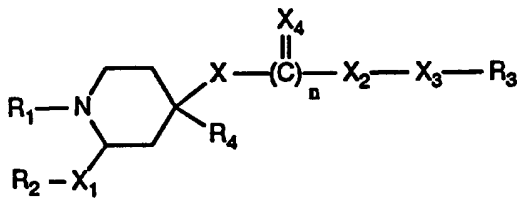
The sodium lauryl sulfate is added to the lyophilised active ingredient through a sieve of 0.2 mm mesh size. The two components are intimately mixed. First the lactose is added through a sieve of 0.6 mm mesh size and then the microcrystalline cellulose is added through a sieve of 0.9 mm mesh size. Then the mixture is intimately mixed again for 10 minutes. Finally the magnesium stearate is added through a sieve of 0.8 mm mesh size. After a further 3 minutes' mixing, the resulting formulation is introduced into size 0 dry-filled gelatin capsules in portions of 390 mg each.

Example 26: Nasal spray:
500 mg of finely ground powder (<5.0 μm) of one of the compounds of formula I mentioned in the preceding Examples, as active ingredient, is suspended in a mixture of 3.5 ml of Myglyol® 812 and 0.08 g of benzyl alcohol. The suspension is introduced into a container having a metering valve. 5.0 g of Freon® 12 are introduced under pressure into the container through the valve. The Freon® is dissolved in the Myglyol®/benzyl alcohol mixture by shaking. The spray container contains approximately 100 single doses which can be administered individually.

Example 27: In a manner analogous to that described in Examples 23 to 26 above, it is also possible to prepare pharmaceutical compositions comprising a different compound of formula I in accordance with one of the above Preparation Examples.

What is claimed is:

1. A novel 1,2,4-trisubstituted piperidine compound of formula I



(I),

wherein

R_1 is an unsubstituted or substituted aralkyl, aryloxyalkyl, heteroaralkyl, aroyl, heteroaroyl, cycloalkylcarbonyl, aralkanoyl, heteroarylalkanoyl, aralkoxycarbonyl or arylcarbamoyl radical, or is the acyl radical of an α-amino acid that is unsubstituted or N-substituted by lower alkanoyl or by carbamoyl-lower alkanoyl,

R_2 is cycloalkyl or an unsubstituted or substituted aryl or heteroaryl radical,

R_3 is an unsubstituted or substituted, optionally hydrogenated aryl or heteroaryl radical or, when n is 1, X_2 is imino that is unsubstituted or substituted by lower alkyl or by cycloalkyl and X_3 is lower alkylene, R_3 is lower alkyl or free or esterified or amidated carboxy,

R_4 is hydrogen, alkyl or aryl,

X is oxy or thio,

X_1 is methylene, ethylene, a direct bond, a free or ketalised carbonyl group or a free or etherified hydroxymethylene group,

X_2 is lower alkylene, imino that is unsubstituted or substituted by lower alkyl or by cycloalkyl, or a direct bond,

X_3 is lower alkylene or a direct bond,

X_4 is oxo or thioxo and

n is 1 or, when X_2 is lower alkylene and X_3 is a direct bond, n is 0,

or a salt thereof.

2. A compound according to claim 1 of formula I wherein

R_1 is a phenyl-, diphenyl-, naphthyl- or fluorenyl-lower alkyl radical that is unsubstituted or substituted in the phenyl moiety by lower alkyl, lower alkoxy, di-lower alkylamino, halogen and/or by trifluoromethyl; a phenoxy-lower alkyl radical that is unsubstituted or substituted in the phenyl moiety by halogen and/or by triazolyl; a heteroaryl-lower alkyl radical containing as heteroaryl radical 6-membered monocyclic azaheteroaryl

or bicyclic azaheteroaryl consisting of a 6-membered and a 5- or 6-membered ring; a benzoyl, naphthoyl, fluorenoyl or 3- to 8-membered cycloalkylcarbonyl radical that is unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, di-lower alkylamino, halogen, cyano and/or by trifluoromethyl; a phenyl- or diphenyl-lower alkanoyl radical that is unsubstituted or substituted in the phenyl moiety by lower alkyl, lower alkoxy, di-lower alkylamino, halogen and/or by trifluoromethyl; a heteroaryl-lower alkanoyl radical containing as heteroaryl radical 6-membered monocyclic azaheteroaryl or bi- or tri-cyclic azaheteroaryl consisting of a 6-membered and one or two 5- or 6-membered ring(s); a phenyl-lower alkoxycarbonyl or N-phenylcarbamoyl radical that is unsubstituted or substituted in the phenyl moiety by lower alkyl, lower alkoxy, di-lower alkylamino, halogen and/or by trifluoromethyl; or the acyl radical of an α-amino acid that occurs naturally as a peptide building block and that is unsubstituted or N-substituted by lower alkanoyl or by carbamoyl-lower alkanoyl,

R_2 is 5- to 7-membered cycloalkyl or a phenyl, naphthyl or 6-membered monocyclic azaheteroaryl radical that is unsubstituted or substituted by aromatically bonded lower alkyl, lower alkoxy, halogen, cyano, nitro, carboxy, carbamoyl and/or by trifluoromethyl,

R_3 is an unsubstituted or lower alkyl-, lower alkoxy-, phenoxy-, halogen-, carboxy-, lower alkoxycarbonyl-, carbamoyl-, cyano- and/or trifluoromethyl-substituted phenyl, cyclohexyl, naphthyl, tetrahydronaphthyl, 5-membered monocyclic oxa- or thia-aryl, 6-membered monocyclic aza- or diaza-aryl or optionally partially hydrogenated heteroaryl radical consisting of a 5- or 6-membered mono- or diaza- or oxa-heteroaryl radical and a 6-membered aryl radical, or, when n is 1, X_2 is unsubstituted or lower alkyl- or cycloalkyl-substituted imino and X_3 is lower alkylene, R_3 is lower alkyl, carboxy, lower alkoxycarbonyl or carbamoyl,

R_4 is hydrogen, lower alkyl or phenyl that is unsubstituted or substituted by lower alkyl, lower alkoxy, phenoxy, halogen, carboxy, lower alkoxycarbonyl, carbamoyl, cyano, nitro and/or by trifluoromethyl,

X is oxy or thio,

X_1 is methylene, ethylene, a carbonyl group that is free or ketalised by a lower alkanol or by a lower alkanediol, a hydroxymethylene group that is free or etherified by a lower alkanol, or is a direct bond;

X_2 is a lower alkylene radical, an imino group that is unsubstituted or substituted by lower alkyl or by 5- to 7-membered cycloalkyl, or is a direct bond;

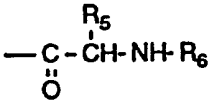
X_3 is lower alkylene or a direct bond;

X_4 is oxo or thioxo, and

n is 1 or, when X_2 is lower alkylene and X_3 is a direct bond, n is 0,
or a salt thereof.

3. A compound according to claim 1 of formula I wherein

R_1 is a phenyl-, diphenyl-, naphthyl- or fluorenyl-lower alkyl radical that is unsubstituted or substituted in the phenyl moiety by lower alkyl, lower alkoxy, di-lower alkylamino, halogen and/or by trifluoromethyl; a phenoxy-lower alkyl radical that is unsubstituted or substituted in the phenyl moiety by halogen and/or by triazolyl; a heteroaryl-lower alkyl radical containing as heteroaryl radical 6-membered monocyclic azaheteroaryl or bicyclic azaheteroaryl consisting of a 6-membered and a 5- or 6-membered ring; a benzoyl, naphthoyl, fluorenoyl or 3- to 8-membered cycloalkylcarbonyl radical that is unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, di-lower alkylamino, halogen, cyano and/or by trifluoromethyl; a phenyl- or diphenyl-lower alkanoyl radical that is unsubstituted or substituted in the phenyl moiety by lower alkyl, lower alkoxy, di-lower alkylamino, halogen and/or by trifluoromethyl; a heteroaryl-lower alkanoyl radical containing as heteroaryl radical 6-membered monocyclic azaheteroaryl or bi- or tri-cyclic azaheteroaryl consisting of a 6-membered and one or two 5- or 6-membered ring(s); a phenyl-lower alkoxycarbonyl or N-phenylcarbamoyl radical that is unsubstituted or substituted in the phenyl moiety by lower alkyl, lower alkoxy, di-lower alkylamino, halogen and/or by trifluoromethyl; or a group of formula Ia



(Ia)

wherein

R_5 is hydrogen, or C_1-C_4alkyl that is unsubstituted or substituted by hydroxy, mercapto, amino, unsubstituted or hydroxy-substituted phenyl, carboxy, carbamoyl or by ureido, and

R_6 is C_2-C_7alkanoyl,

R_2 is 5- to 7-membered cycloalkyl, or a phenyl, naphthyl or 6-membered monocyclic azaheteroaryl radical that is unsubstituted or substituted by aromatically bonded lower alkyl, lower alkoxy, halogen, cyano, nitro and/or by trifluoromethyl,

R_3 is a phenyl, naphthyl or pyridyl radical that is unsubstituted or substituted by lower alkyl, lower alkoxy, halogen and/or by trifluoromethyl, or a heteroaryl radical, consisting of an optionally partially hydrogenated 5- or 6-membered mono- or diaza- or oxa-heteroaryl radical and a 6-membered aryl radical, that is unsubstituted or

C-substituted by lower alkyl, lower alkoxy, halogen and/or by trifluoromethyl and unsubstituted or N-substituted by lower alkanol,

X is oxy or thio,

X_1 is methylene, ethylene, a carbonyl group that is free or ketalised by a lower alkanol or by a lower alkanediol, a hydroxymethylene group that is free or etherified by a lower alkanol, or is a direct bond,

X_2 is a lower alkylene radical, an imino group that is unsubstituted or substituted by lower alkyl or by 5- to 7-membered cycloalkyl, or is a direct bond,

X_3 is a direct bond,

X_4 is oxo, and

n is 1 or, when X_2 is a lower alkylene radical, n is 0,

or a salt thereof.

4. A compound according to claim 1 of formula I wherein

R_1 is benzoyl that is unsubstituted or substituted by C_1-C_4alkyl, C_1-C_4alkoxy, di-C_1-C_4alkylamino, halogen and/or by trifluoromethyl, or is unsubstituted naphthoyl,

R_2 is phenyl that is unsubstituted or substituted by C_1-C_4alkyl, C_1-C_4alkoxy, halogen, cyano, nitro, carboxy, carbamoyl and/or by trifluoromethyl,

R_3 is phenyl or naphthyl that is unsubstituted or substituted by C_1-C_4alkyl, C_1-C_4alkoxy, phenoxy, halogen, carboxy, C_1-C_4alkoxycarbonyl, carbamoyl, cyano and/or by trifluoromethyl, or is unsubstituted pyridyl, benzofuranyl, unsubstituted or C_1-C_4alkyl-N-substituted indolyl or 2,3-dihydroindolyl, benzimidazolyl, quinolyl or 1,2,3,4-tetrahydroquinolinyl, or, when n is 1, X_2 is imino that is unsubstituted or substituted by C_1-C_4alkyl and X_3 is C_1-C_4alkylene, R_3 is C_1-C_7alkyl, carboxy, C_1-C_4alkoxycarbonyl or carbamoyl,

R_4 is hydrogen or C_1-C_4alkyl,

X is oxy or thio,

X_1 is methylene,

X_2 is C_1-C_4alkylene, imino, C_1-C_4alkylimino or a direct bond,

X_3 is C_1-C_4alkylene or a direct bond,

X_4 is oxo or thioxo, and

n is 1 or, when X_2 is C_1-C_4alkylene and X_3 is a direct bond, n is 0,

or a salt thereof.

5. A compound according to claim 1 of formula I wherein

R_1 is benzoyl that is unsubstituted or substituted by C_1-C_4alkyl, C_1-C_4alkoxy, di-

C_1-C_4alkylamino, halogen and/or by trifluoromethyl,

R_2 is phenyl that is unsubstituted or substituted by C_1-C_4alkyl, C_1-C_4alkoxy, halogen, cyano, nitro, carboxy, carbamoyl and/or by trifluoromethyl,

R_3 is indolyl that is unsubstituted or N-substituted by C_1-C_4alkyl, or is unsubstituted quinolyl or 1,2,3,4-tetrahydroquinolinyl,

R_4 is hydrogen,

X is oxy,

X_1 is methylene,

X_2 is C_1-C_4alkylene, imino or a direct bond,

X_3 is methylene or a direct bond,

X_4 is oxo or thioxo, and

n is 1 or, when X_2 is C_1-C_4alkylene and X_3 is a direct bond, n is 0,

or a salt thereof.

6. A compound according to claim 3 of formula I wherein

R_1 is benzoyl that is unsubstituted or substituted by C_1-C_4alkyl, C_1-C_4alkoxy, di-C_1-C_4alkylamino, halogen and/or by trifluoromethyl,

R_2 is phenyl that is unsubstituted or substituted by C_1-C_4alkyl, C_1-C_4alkoxy, halogen, cyano, nitro and/or by trifluoromethyl,

R_3 is unsubstituted quinolyl or 1,2,3,4-tetrahydroquinolinyl,

R_4 is hydrogen,

X is oxy or thio,

X_1 is methylene,

X_2 is C_1-C_4alkylene, imino or a direct bond,

X_3 is a direct bond,

X_4 is oxo, and

n is 1 or, when X_2 is C_1-C_4alkylene, n is 0,

or a salt thereof.

7. (2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-(4-quinolylmethoxy)-piperidine or a salt thereof.

8. (2R*,4S*)-quinoline-3-carboxylic acid [2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-piperidin-4-yl] ester or a salt thereof.

9. (2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-(3-quinolylmethoxy)-piperid-

ine or a salt thereof.

10. (2R*,4S*)-quinoline-4-carboxylic acid [2-benzyl-1-(3,5-bis(trifluoromethyl)benzoyl)-piperidin-4-yl] ester or a salt thereof.

11. (2R*,4S*)-3,5-dimethoxyphenylacetic acid [2-benzyl-1-(3,5-bis(trifluoromethyl)-benzoyl)-piperidin-4-yl] ester or a salt thereof.

12. (2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-(N-phenylcarbamoyloxy)-piperidine or a salt thereof.

13. (2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-[N-(1-naphthyl)carbamoyl-oxy]-piperidine or a salt thereof.

14. (2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-[N-(3-trifluoromethyl-phenyl)carbamoyloxy]-piperidine or a salt thereof.

15. (2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-[N-(2,4-difluorophenyl)-carbamoyloxy]-piperidine or a salt thereof.

16. (2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-(N-cyclohexylcarbamoyl-oxy)-piperidine or a salt thereof.

17. (2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-[N-(3-methoxy)-phenyl)-carbamoyloxy]-piperidine or a salt thereof.

18. (2S*,4R*,1'R)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-{N-[2-(1-naphthyl)-ethyl]carbamoyloxy}-piperidine or a salt thereof.

19. (2R*,4S*,1'R)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-{N-[2-(1-naphthyl)-ethyl]carbamoyloxy}-piperidine or a salt thereof.

20. (2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-[N-(4-phenoxy)phenyl)-carbamoyloxy]-piperidine or a salt thereof.

21. (2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-[N-(4-isopropyloxy)phenyl)-

carbamoyloxy]-piperidine or a salt thereof.

22. (2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-[N-(3-isopropyloxy-phenyl)-carbamoyloxy]-piperidine or a salt thereof.

23. (2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-[N-(1-naphthyl)thiocarbam-oyloxy]-piperidine or a salt thereof.

24. (2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-[N-(4-phenoxyphenyl)thio-carbamoyloxy]-piperidine or a salt thereof.

25. (2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-[N-(4-ethoxycarbonyl-phenyl)thiocarbamoyloxy]-piperidine or a salt thereof.

26. (2R*,4S*)-phenylacetic acid [2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-piperidin-4-yl] ester or a salt thereof.

27. (2R*,4S*)-[2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-piperidin-4-yl]-thioether or a salt thereof.

28. (2R*,4S*)-2-(4-nitrobenzyl)-1-(3,5-dimethylbenzoyl)-4-formyloxy-piperidine;

(2R*,4S*)-2-(2,4-dichlorobenzyl)-1-(3,5-dimethylbenzoyl)-4-formyloxy-piperidine;

(2R*,4S*)-2-(3,4-dichlorobenzyl)-1-(3,5-dimethylbenzoyl)-4-formyloxy-piperidine;

(2R*,4S*)-2-(4-methoxybenzyl)-1-(3,5-dimethylbenzoyl)-4-formyloxy-piperidine;

(2R*,4S*)-2-(2,4-dimethoxybenzyl)-1-(3,5-dimethylbenzoyl)-4-formyloxy-piperidine;

(2R*,4S*)-2-(4-carboxybenzyl)-1-(3,5-dimethylbenzoyl)-4-formyloxy-piperidine;

(2R*,4S*)-2-(4-carboxamidobenzyl)-1-(3,5-dimethylbenzoyl)-4-formyloxy-piperidine;

(2R*,4S*)-2-(4-nitrobenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-formyloxy-piperidine;

(2R*,4S*)-2-(2,4-dichlorobenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-formyloxy-piperidine;

(2R*,4S*)-2-(3,4-dichlorobenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-formyloxy-piperidine;

(2R*,4S*)-2-(4-methoxybenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-formyloxy-piperidine;

(2R*,4S*)-2-(2,4-dimethoxybenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-formyloxy-piperidine;

(2R*,4S*)-2-(4-carboxybenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-formyloxy-piperidine;

(2R*,4S*)-2-(4-carboxamidobenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-formyloxy-piperidine;

(2R*,4S*)-2-(4-nitrobenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-(4-quinolinylmethoxy)-piperidine;

(2R*,4S*)-2-(2,4-dichlorobenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-(4-quinolinylmethoxy)-piperidine;

(2R*,4S*)-2-(3,4-dichlorobenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-(4-quinolinylmethoxy)-piperidine;

(2R*,4S*)-2-(4-methoxybenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-(4-quinolinylmethoxy)-piperidine;

(2R*,4S*)-2-(2,4-dimethoxybenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-(4-quinolinylmethoxy)-piperidine;

(2R*,4S*)-2-(4-carboxybenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-(4-quinolinylmethoxy)-piperidine;

(2R*,4S*)-2-(4-carboxamidobenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-(4-quinolinyl-methoxy)-piperidine;

(2R*,4S*)-2-(4-nitrobenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-(3-quinolinylmethoxy)-piperidine;

(2R*,4S*)-2-(2,4-dichlorobenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-(3-quinolinyl-methoxy)-piperidine;

(2R*,4S*)-2-(3,4-dichlorobenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-(3-quinolinyl-methoxy)-piperidine;

(2R*,4S*)-2-(4-methoxybenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-(3-quinolinyl-methoxy)-piperidine;

(2R*,4S*)-2-(2,4-dimethoxybenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-3-(3-quinolinyl-methoxy)-piperidine;

(2R*,4S*)-2-(4-carboxybenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-(3-quinolinyl-methoxy)-piperidine;

(2R*,4S*)-2-(4-carboxamidobenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-(3-quinolinyl-methoxy)-piperidine;

(2R*,4S*)-quinoline-3-carboxylic acid [2-(4-nitrobenzyl)-1-(3,5-bistrifluoromethyl-benzoyl)-piperidin-4-yl] ester;

(2R*,4S*)-quinoline-3-carboxylic acid [2-(2,4-dichlorobenzyl)-1-(3,5-bistrifluoromethyl-benzoyl)-piperidin-4-yl] ester;

(2R*,4S*)-quinoline-3-carboxylic acid [2-(3,4-dichlorobenzyl)-1-(3 ,5-bistrifluoromethyl-benzoyl)-piperidin-4-yl] ester;

(2R*,4S*)-quinoline-3-carboxylic acid [2-(4-methoxybenzyl)-1-(3,5-bistrifluoromethyl-benzoyl)-piperidin-4-yl] ester;

(2R*,4S*)-quinoline-3-carboxylic acid [2-(2,4-dimethoxybenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-piperidin-4-yl]-ester;

(2R*,4S*)-quinoline-3-carboxylic acid [2-(4-carboxybenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-piperidin-4-yl] ester;

(2R*,4S*)-quinoline-3-carboxylic acid [2-(4-carboxamidobenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-piperidin-4-yl] ester;

(2R*,4S*)-quinoline-4-carboxylic acid [2-(4-nitrobenzyl)-1-(3,5-bistrifluoromethyl)-benzoyl)-piperidin-4-yl] ester;

(2R*,4S*)-quinoline-4-carboxylic acid [2-(2,4-dichlorobenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-piperidin-4-yl] ester;

(2R*,4S*)-quinoline-4-carboxylic acid [2-(3,4-dichlorobenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-piperidin-4-yl] ester;

(2R*,4S*)-quinoline-4-carboxylic acid [2-(4-methoxybenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-piperidin-4-yl] ester;

(2R*,4S*)-quinoline-4-carboxylic acid [2-(2,4-dimethoxybenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-piperidin-4-yl] ester;

(2R*,4S*)-quinoline-4-carboxylic acid [2-(4-carboxybenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-piperidin-4-yl] ester;

(2R*,4S*)-quinoline-4-carboxylic acid [2-(4-carboxamidobenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-piperidin-4-yl] ester;

(2R*,4S*)-1-methyl-2-indolecarboxylic acid [2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-piperidin-4-yl] ester;

(2R*,4S*)-3,5-dimethoxyphenylacetic acid [2-benzyl-1-(3,5-dimethylbenzoyl)-piperidin-4-yl] ester;

(2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-(N-benzylcarbamoyloxy)-piperidine;

(2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-[N-(3-cyanophenyl)carbamoyloxy]-piperidine;

(2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-(N-heptyl)carbamoyloxy)-piperidine;

(2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-(N-diisopropylcarbamoyloxy)-piperidine;

(2R*,4S*)-[2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-piperidin-4-yloxycarbonylamino]-acetic acid ethyl ester;

(2R*,4S*)-[2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-[N-ethoxycarbonylcarbamoyloxy]-piperidine;

(2R*,4S*)-[2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-[N-ethoxycarbonylthiocarbamoyloxy]-piperidine;

(2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-(4-quinolylmethylthio)-piperidine

or

(2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-(3-quinolylmethylthio)-piperidine

or a salt thereof in each case.

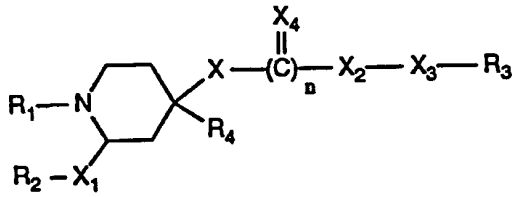
29. A compound according to any one of claims 1 to 28 for use in a method for the therapeutic treatment of the human or animal body.

30. A pharmaceutical composition comprising as pharmaceutical active ingredient, in addition to customary pharmaceutical excipients, a compound according to any one of

claims 1 to 29 in free form or in the form of a pharmaceutically acceptable salt.

31. A pharmaceutical composition comprising as pharmaceutical active ingredient, in addition to customary pharmaceutical excipients, a compound according to any one of claims 3 and 6 to 11 in free form or in the form of a pharmaceutically acceptable salt.

32. A process for the preparation of a novel 1,2,4-trisubstituted piperidine compound of formula I



(I),

wherein

R_1 is an unsubstituted or substituted aralkyl, aryloxyalkyl, heteroaralkyl, aroyl, heteroaroyl, cycloalkylcarbonyl, aralkanoyl, heteroarylalkanoyl, aralkoxycarbonyl or arylcarbamoyl radical, or is the acyl radical of an α-amino acid that is unsubstituted or N-substituted by lower alkanoyl or by carbamoyl-lower alkanoyl,

R_2 is cycloalkyl or an unsubstituted or substituted aryl or heteroaryl radical,

R_3 is an unsubstituted or substituted, optionally hydrogenated aryl or heteroaryl radical or, when n is 1, X_2 is imino that is unsubstituted or substituted by lower alkyl or by cycloalkyl and X_3 is lower alkylene, R_3 is lower alkyl or free or esterified or amidated carboxy,

R_4 is hydrogen or alkyl,

X is oxy or thio,

X_1 is methylene, ethylene, a direct bond, a free or ketalised carbonyl group or a free or etherified hydroxymethylene group,

X_2 is lower alkylene, imino that is unsubstituted or substituted by lower alkyl or by cycloalkyl, or a direct bond,

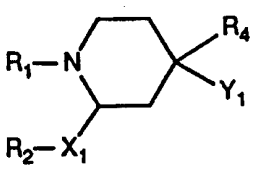
X_3 is lower alkylene or a direct bond,

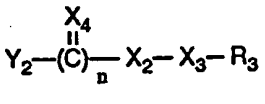
X_4 is oxo or thioxo and

n is 1 or, when X_2 is lower alkylene and X_3 is a direct bond, n is 0,

or a salt thereof, which process comprises

a) condensing with one another compounds of formulae II and III



(II) and  (III),

wherein

R_1, R_2, R_3, R_4, X_1, X_2, X_3, X_4 and n are as defined and

one of the radicals Y_1 and Y_2 is hydroxy or mercapto, optionally in the form of a salt, and the other is hydroxy or reactive esterified hydroxy or, when n is 1, etherified hydroxy,

or wherein

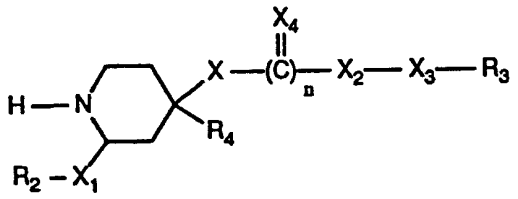
R_1, R_2, R_3, R_4, X_1, X_2, X_3 and X_4 are as defined,

Y_1 is hydroxy esterified by a carboxylic acid,

Y_2 is hydroxy that is free or etherified or in the form of a salt, and

n is 1, or

b) introducing the radical R_1 into a compound of formula IV



(IV),

wherein

R_2, R_3, R_4, X, X_1, X_2, X_3 and n are as defined,

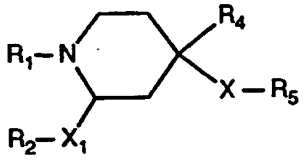
and, if desired, converting a resulting compound into a different compound of formula I, separating a mixture of isomers obtainable in accordance with the process into its components and isolating the preferred isomer, and/or converting a free compound obtainable in accordance with the process into a salt or converting a salt obtainable in accordance with the process into the corresponding free compound.

33. A method for the prophylactic and therapeutic treatment of diseases in which compound P plays an essential role, which method comprises administering to a warm-blooded animal requiring treatment a compound according to any one of claims 1 to 28 or a pharmaceutically acceptable salt thereof or a pharmaceutical composition according to either claim 29 or claim 30.

34. A method of treatment according to claim 33 for the treatment of painful conditions, migraines, disorders of the central nervous system, certain motor disorders, inflammatory diseases, diseases of the respiratory organs, diseases of the gastrointestinal system, vomiting and/or hypertension, which method comprises administering to a warm-blooded animal requiring treatment a compound according to any one of claims 1 to 28 or a pharmaceutically acceptable salt thereof or a pharmaceutical composition according to either claim 29 or claim 30.

35. The use of a compound according to any one of claims 1 to 28 in a method for the treatment of diseases in which compound P plays an essential role, or in the manufacture of a medicament intended therefor.

36. A compound of formula V



(V),

wherein

R_1 is an unsubstituted or substituted aralkyl, aryloxyalkyl, heteroaralkyl, aroyl, heteroaroyl, cycloalkylcarbonyl, aralkanoyl, heteroarylalkanoyl, aralkoxycarbonyl or arylcarbamoyl radical, or is the acyl radical of an α-amino acid that is unsubstituted or N-substituted by lower alkanoyl or by carbamoyl-lower alkanoyl,

R_2 is cycloalkyl or an unsubstituted or substituted aryl or heteroaryl radical,

R_4 is hydrogen or alkyl,

R_5 is hydrogen, formyl or carbamoyl,

X is oxy or thio,

X_1 is methylene, ethylene, a direct bond, a free or ketalised carbonyl group or a free or etherified hydroxymethylene group,

or a salt thereof.

37. A compound according to claim 36 of formula V wherein

R_1 is a phenyl-, diphenyl-, naphthyl- or fluorenyl-lower alkyl radical that is unsubstituted or substituted in the phenyl moiety by lower alkyl, lower alkoxy, di-lower alkylamino, halogen and/or by trifluoromethyl; a phenoxy-lower alkyl radical that is unsubstituted

or substituted in the phenyl moiety by halogen and/or by triazolyl; a heteroaryl-lower alkyl radical containing as heteroaryl radical 6-membered monocyclic azaheteroaryl or bicyclic azaheteroaryl consisting of a 6-membered and a 5- or 6-membered ring; a benzoyl, naphthoyl, fluorenoyl or 3- to 8-membered cycloalkylcarbonyl radical that is unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, di-lower alkylamino, halogen, cyano and/or by trifluoromethyl; a phenyl- or diphenyl-lower alkanoyl radical that is unsubstituted or substituted in the phenyl moiety by lower alkyl, lower alkoxy, di-lower alkylamino, halogen and/or by trifluoromethyl; a heteroaryl-lower alkanoyl radical containing as heteroaryl radical 6-membered monocyclic azaheteroaryl or bi- or tri-cyclic azaheteroaryl consisting of a 6-membered and one or two 5- or 6-membered ring(s); a phenyl-lower alkoxycarbonyl or N-phenylcarbamoyl radical that is unsubstituted or substituted in the phenyl moiety by lower alkyl, lower alkoxy, di-lower alkylamino, halogen and/or by trifluoromethyl; or the acyl radical of an α-amino acid that occurs naturally as a peptide building block and that is unsubstituted or N-substituted by lower alkanoyl or by carbamoyl-lower alkanoyl,

R_2 is 5- to 7-membered cycloalkyl or a phenyl, naphthyl or 6-membered monocyclic azaheteroaryl radical that is unsubstituted or substituted by aromatically bonded lower alkyl, lower alkoxy, halogen, cyano, nitro, carboxy, carbamoyl and/or by trifluoromethyl,

R_4 is hydrogen or alkyl,

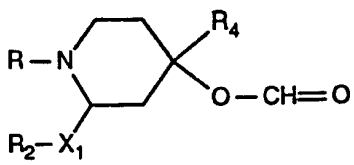
R_5 is hydrogen or formyl,

X is oxy or thio,

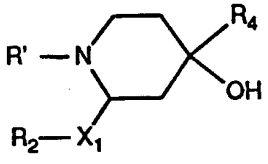
X_1 is methylene, ethylene, a carbonyl group that is free or ketalised by a lower alkanol or by a lower alkanediol, a hydroxymethylene group that is free or etherified by a lower alkanol, or a direct bond,

or a salt thereof.

38. A compound according to claim 36 of formulae IIc and IId



(IIc) and



(IId),

wherein

R_1 is benzoyl that is unsubstituted or substituted by C_1-C_4alkyl, C_1-C_4alkoxy, di-C_1-C_4alkylamino, halogen and/or by trifluoromethyl, or is unsubstituted naphthoyl,

R_2 is phenyl that is unsubstituted or substituted by C_1-C_4alkyl, C_1-C_4alkoxy, halogen, cyano, nitro, carboxy, carbamoyl and/or by trifluoromethyl,
R_4 is hydrogen or alkyl,
R_5 is hydrogen or formyl, and
X_1 is methylene,
or a salt thereof.

39. A compound according to claim 36 of formulae IIb and IIc wherein
R is benzoyl that is unsubstituted or substituted by C_1-C_4alkyl, C_1-C_4alkoxy, di-C_1-C_4alkylamino, halogen and/or by trifluoromethyl,
R_2 is phenyl that is unsubstituted or substituted by C_1-C_4alkyl, C_1-C_4alkoxy, halogen, cyano, nitro, carboxy, carbamoyl and/or by trifluoromethyl,
R_4 is hydrogen,
R_5 is hydrogen or formyl, and
X_1 is methylene,
or a salt thereof.

40. (2R*,4S*)-2-(4-chlorobenzyl)-1-(3,5-dimethylbenzoyl)-4-formyloxy-piperidine or a salt thereof.

41. (2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-hydroxy-piperidine or a salt thereof.

42. (2R*,4S*)-2-(4-nitrobenzyl)-1-(3,5-dimethylbenzoyl)-4-formyloxy-piperidine;

(2R*,4S*)-2-(2,4-dichlorobenzyl)-1-(3,5-dimethylbenzoyl)-4-formyloxy-piperidine;

(2R*,4S*)-2-(3,4-dichlorobenzyl)-1-(3,5-dimethylbenzoyl)-4-formyloxy-piperidine;

(2R*,4S*)-2-(4-methoxybenzyl)-1-(3,5-dimethylbenzoyl)-4-formyloxy-piperidine;

(2R*,4S*)-2-(2,4-dimethoxybenzyl)-1-(3,5-dimethylbenzoyl)-4-formyloxy-piperidine;

(2R*,4S*)-2-(4-carboxybenzyl)-1-(3,5-dimethylbenzoyl)-4-formyloxy-piperidine;

(2R*,4S*)-2-(4-carboxamidobenzyl)-1-(3,5-dimethylbenzoyl)-4-formyloxy-piperidine;

(2R*,4S*)-2-(4-nitrobenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-formyloxy-piperidine;

(2R*,4S*)-2-(2,4-dichlorobenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-formyloxy-piperidine;

(2R*,4S*)-2-(3,4-dichlorobenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-formyloxy-piperidine;

(2R*,4S*)-2-(4-methoxybenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-formyloxy-piperidine;

(2R*,4S*)-2-(2,4-dimethoxybenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-formyloxy-piperidine;

(2R*,4S*)-2-(4-carboxybenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-formyloxy-piperidine;

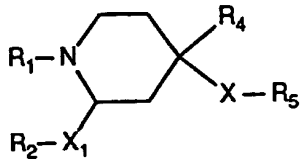
(2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-(1-heptyl)-4-carbamoyloxy-piperidine;

(2R*,4S*)-2-benzyl-1-(3,5-bistrifluoromethylbenzoyl)-4-(1-heptyl)-carbamoyloxy-piperidine or

(2R*,4S*)-2-(4-carboxamidobenzyl)-1-(3,5-bistrifluoromethylbenzoyl)-4-formyloxy-piperidine

or a salt thereof in each case.

43. A process for the preparation of a compound of formula V



(V),

wherein

R_1 is an unsubstituted or substituted aralkyl, aryloxyalkyl, heteroaralkyl, aroyl, heteroaroyl, cycloalkylcarbonyl, aralkanoyl, heteroarylalkanoyl, aralkoxycarbonyl or arylcarbamoyl radical, or is the acyl radical of an α-amino acid that is unsubstituted or N-substituted by lower alkanoyl or by carbamoyl-lower alkanoyl,

R_2 is cycloalkyl or an unsubstituted or substituted aryl or heteroaryl radical,

R_4 is hydrogen or alkyl, and

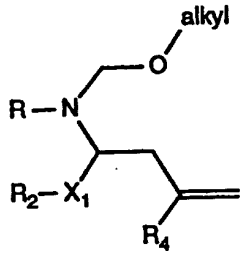
R_5 is hydrogen, formyl or carbamoyl,

X is oxy, and

X_1 is methylene, ethylene, a direct bond, a free or ketalised carbonyl group or a free or etherified hydroxymethylene group,

or a salt thereof,

which process comprises subjecting a compound of formula IIb



(IIb),

wherein

alkyl is alkyl, especially lower alkyl, and

R is a group R_1, and

R_1, R_2, R_4 and X_1 are each as defined for compounds of formula I,

to intramolecular condensation and subjecting the resulting compound of formula V wherein R_5 is formyl to acid hydrolysis to form the corresponding compound of formula V wherein R_5 is hydrogen.

44. The use of a compound according to any one of claims 36 to 40 as an intermediate in the preparation of compounds of formula I according to any one of claims 1 to 29.

INTERNATIONAL SEARCH REPORT

Interna ! Application No
PCT/EP 94/03394

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D401/12 C07D211/46 A61K31/445 C07D211/54

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TETRAHEDRON LETTERS., vol.33, no.22, 1992, OXFORD GB pages 3133 - 3136 see RN 142913-87-9, 1,3-Dioxolane-4-carboxaldehyde, 5-[4-hydroxy-1-(phenylmethyl)-2- piperidinyl]-2,2-dimethyl-, [2S-[2.alpha.(4R*,5S*),4.alpha.]]- see RN 142913-85-7, 4-Piperidinol, 1-(phen ylmethyl)-2-(2,2,2',2'-tetramethyl[4,4'-bi -1,3- dioxolan]-5-yl)-, [2S-[2.alpha.[4R*(S*),5S*],4.alpha.]]- (9CI) see RN 142913-86-8, 1,2-Ethanediol, 1-[5-[4-hydroxy-1-(phenylmethyl)-2-piperidinyl]- 2,2- dimethyl-1,3-dioxolan-4-yl]-, [2S-[2.alpha.[4S*(S*),5S*],4.alpha.]]- see page 3134 --- -/--	36

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 January 1995	- 9. 02. 95
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Authorized officer Kissler, B

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INTERNATIONAL SEARCH REPORT

Interna l Application No
PCT/EP 94/03394

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOURNAL OF MEDICINAL CHEMISTRY., vol.35, no.3, 1992, WASHINGTON US pages 490 - 501 se RN 138155-48-3, 4-Piperidinol, 1-[(3,4-dichlorophenyl)acetyl]-2-(1-pyrrolidinylmethyl)-, trans-(.+-.)-, (Z)-2-butenedioate (1:1) (salt) see RN 138155-47-2, 4-Piperidinol, 1-[(3,4-dichlorophenyl)acetyl]-2-(1-pyrrolidinylmethyl)-, monohydrochloride, cis-(.+-.)- see RN 138155-00-7, 4-Piperidinol, 1-[(3,4-dichlorophenyl)acetyl]-2-(1-pyrrolidinylmethyl)-, trans-(.+-.) ---	36
X	EP,A,0 330 461 (GLAXO) 30 August 1989 see RN 125104-56-5, 4-Piperidinol, 1-[(3,4-dichlorophenyl)acetyl]-2-(1-pyrrolidinylmethyl)-, cis- see RN 125104-54-3, 4-Piperidinol, 1-[(3,4-dichlorophenyl)acetyl]-2-(1-pyrrolidinylmethyl)-, trans-, (Z)-2-butenedioate (1:1) (salt) see claim 1 ---	36,37
A	EP,A,0 528 495 (MERCK SHARP & DOHME) 24 February 1993 see the whole document -----	1-44

1

INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/EP 94/ 03394

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 33-35 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna l Application No
PCT/EP 94/03394

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0330461	30-08-89	AU-A-	3029589	24-08-89
		JP-A-	1308250	12-12-89
		PT-B-	89779	29-04-94
EP-A-0528495	24-02-93	AU-A-	2413892	16-03-93
		CA-A-	2112397	04-03-93
		EP-A-	0600952	15-06-94
		WO-A-	9304040	04-03-93
		JP-T-	6510034	10-11-94